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Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Eighth Special Issue

Anand Padmanabhan[1] | Laura Connelly-Smith[2] | Nicole Aqui[3] | Rasheed A. Balogun[4] | Reinhard Klingel[5] | Erin Meyer[6] | Huy P. Pham[7] | Jennifer Schneiderman[8] | Volker Witt[9] | Yanyun Wu[10] | Nicole D. Zantek[11] | Nancy M. Dunbar[12] |

Guest Editor: Joseph Schwartz[13]

[1]Medical Sciences Institute & Blood Research Institute, Versiti & Department of Pathology, Medical College of Wisconsin, Milwaukee, Wisconsin

[2]Department of Medicine, Seattle Cancer Care Alliance & University of Washington, Seattle, Washington

[3]Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

[4]Department of Medicine, University of Virginia, Charlottesville, Virginia

[5]Apheresis Research Institute, Cologne, Germany & First Department of Internal Medicine, University of Mainz, Mainz, Germany

[6]Department of Hematology/Oncology/BMT/Pathology, Nationwide Children's Hospital, Columbus, Ohio

[7]Department of Pathology, Keck School of Medicine of the University of Southern California, Los Angeles, California

[8]Department of Pediatric Hematology/Oncology/Neuro-oncology/Stem Cell Transplant, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University, Chicago, Illinois

[9]Department for Pediatrics, St. Anna Kinderspital, Medical University of Vienna, Vienna, Austria

[10]Bloodworks NW & Department of Laboratory Medicine, University of Washington, Seattle, Washington, Yale University School of Medicine, New Haven, Connecticut

[11]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota

[12]Department of Pathology and Laboratory Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire

[13]Department of Pathology and Cell Biology, Columbia University Medical Center, New York, New York

Correspondence
Nancy M. Dunbar, MD; Dartmouth-Hitchcock Medical Center, Lebanon, NH 03756.
Email: nancy.m.dunbar@hitchcock.org

ABSTRACT

The American Society for Apheresis (ASFA) Journal of Clinical Apheresis (JCA) Special Issue Writing Committee is charged with reviewing, updating and categorizing indications for the evidence-based use of therapeutic apheresis (TA) in human disease. Since the 2007 JCA Special Issue (Fourth Edition), the committee has incorporated systematic review and evidence-based approaches in the grading and categorization of apheresis indications. This Eighth Edition of the JCA Special Issue continues to maintain this methodology and rigor in order to make recommendations on the use of apheresis in a wide variety of diseases/conditions. The JCA Eighth Edition, like its predecessor, continues to apply the category and grading system definitions in fact sheets. The general layout and concept of a fact sheet that was introduced in the Fourth Edition, has largely been maintained in this edition. Each fact sheet succinctly

summarizes the evidence for the use of TA in a specific disease entity or medical condition. The Eighth Edition comprises 84 fact sheets for relevant diseases and medical conditions, with 157 graded and categorized indications and/or TA modalities. The Eighth Edition of the JCA Special Issue seeks to continue to serve as a key resource that guides the utilization of TA in the treatment of human disease.

1 | INTRODUCTION

The Writing Committee of the Journal of Clinical Apheresis (JCA) Special Issue 2019 is pleased to present the Eighth Edition of the JCA Special Issue. After more than 2 years of engaging collaborative work, and the rigorous critical review of fact sheets contained herein, we believe that this document will appeal to both practitioners with a focus in the area of apheresis medicine and other physicians who may need to utilize therapeutic apheresis (TA) occasionally for the care of their patients. This latest iteration of evidence-based ASFA categories is based upon a stringent review of up-to-date literature, analysis of the quality of evidence, and the strength of recommendation derived from this evidence.

This Special Issue is a compilation of fact sheets for 84 diseases (Table 1). To clarify terminology used in this table and throughout this document, **"Disease"** refers to a specific disease or medical condition (e.g., myasthenia gravis [disease]; transplantation, liver [medical condition]) and represents the pathology discussed in the fact sheet. **"Indication"** refers to the use of apheresis in specific situations encountered in the disease (e.g. acute, short-term treatment [indication]). Each disease, TA modality and indication is assigned a category (Table 2) and grade (Table 3) as in previous editions. In this edition, we have continued to use the table format at the start of each fact sheet to summarize disease name, TA modality (Table 4), indication(s), category, and grade. Several diseases or conditions that are category IV, which have been described in detail in previous editions and do not have significant new evidence since the last publication, are summarized in a separate table (Table 5).

The 2019 JCA Special Issue Writing Committee comprised 13 members from diverse fields including Transfusion Medicine/Apheresis, Hematology/Oncology, Pediatrics, Nephrology, and Critical Care Medicine from locations across the United States and Europe. Each disease or condition was assigned to one committee member as primary author. That primary author reviewed any new developments in the understanding, current management, and treatment of the disease or condition as well as any changes in the evidence surrounding the use of TA as a treatment modality. Only peer-reviewed PubMed-indexed publications available in English were considered when reviewing literature published since the last fact sheet update. The primary author updated each fact sheet table, disease description, current management, rationale for TA, technical notes (e.g., volumes treated, frequency, replacement fluid), duration and discontinuation of treatment, and provided a maximum of 20 key references highlighting important or new studies and/or reviews (Figure 1). Two other committee members, along with an external expert for select fact sheets, provided secondary peer-review of each fact sheet. The entire writing committee performed a third and final review of all fact sheets with category and grade assigned by consensus in the same manner as described in previous editions with consistent application of evaluation criteria. This evidence-based approach is designed to achieve several objectives. First, it provides uniformity to ASFA category assignment and disease discussion while minimizing personal bias. Second, it provides the strength of recommendation [strong (1) vs. weak (2)] using a defined grading schema. Finally, it provides comprehensive, yet succinct information easily shared with healthcare providers requesting information on the potential utility of apheresis in a given clinical setting. The entire process of fact sheet development is shown in Figure 2.

Several diseases or conditions underwent review in consideration for the development of a new fact sheet (Table 6). To meet criteria for a new fact sheet, the committee required a minimum of 10 cases published in the last decade in peer-reviewed journals, ideally by more than one group. Based on these criteria, there were no new disease categories added to the JCA 2019 Special Issue. Strong consideration was given for the addition of a new fact sheet on Alzheimer's disease. The published evidence for the use of TPE in Alzheimer's disease is currently limited. Preliminary data from the recently concluded phase IIb/III Alzheimer Management by Albumin Replacement (AMBAR) study is available in abstract form but is not yet published in a peer-reviewed journal. Thus, Alzheimer's disease was not selected for inclusion in the JCA 2019 Special Issue.

Some previously published fact sheets were renamed to group fact sheets together by similar disease pathology and/or treatment. For example, "ANCA-associated rapidly progressive glomerulonephritis" and "Henoch-Schönlein purpura" were renamed "Vasculitis, ANCA-associated" and "Vasculitis, IgA (Henoch-Schönlein purpura)" respectively with a separate fact sheet for "Vasculitis, other." All fact sheets involving transplantation have been renamed "Transplantation, transplant-type…" The "Aplastic anemia, pure red cell aplasia" fact sheet

TABLE 1 Category and Grade Recommendations for Therapeutic Apheresis

Disease	TA modality	Indication	Category	Grade	Page
Acute disseminated encephalomyelitis (ADEM)	TPE	Steroid Refractory	II	2C	187
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)	TPE	Primary Treatment	I	1A	189
	IA	Primary Treatment	I	1B	
Acute liver failure	TPE-HV		I	1A	191
	TPE		III	2B	
Age related macular degeneration, dry	Rheopheresis	High-risk	II	2B	193
Amyloidosis, systemic	ß2-microglobulin column	Dialysis-related amyloidosis	II	2B	195
	TPE	Other causes	IV	2C	
Anti-glomerular basement membrane disease (Goodpasture syndrome)	TPE	Diffuse alveolar hemorrhage (DAH)	I	1C	197
	TPE	Dialysis- independence	I	1B	
	TPE	Dialysis-dependence, no DAH	III	2B	
Atopic (neuro-) dermatitis (atopic eczema), recalcitrant	ECP		III	2A	199
	IA		III	2C	
	TPE/DFPP		III	2C	
Autoimmune hemolytic anemia, severe	TPE	Severe cold agglutinin disease	II	2C	201
	TPE	Severe warm autoimmune	III	2C	
Babesiosis	RBC exchange	Severe	II	2C	203
Burn shock resuscitation	TPE		III	2B	205
Cardiac neonatal lupus	TPE		III	2C	207
Catastrophic antiphospholipid syndrome (CAPS)	TPE		I	2C	209
Chronic focal encephalitis (Rasmussen Encephalitis)	TPE		III	2C	211
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	TPE/IA		I	1B	213
Coagulation factor inhibitors	TPE		III	2C	215
	IA		III	2B	
Complex regional pain syndrome	TPE	Chronic	III	2C	217
Cryoglobulinemia	TPE	Severe/symptomatic	II	2A	219
	IA	Severe/symptomatic	II	2B	
Cutaneous T cell lymphoma (CTCL); Mycosis fungoides; Sézary syndrome	ECP	Erythrodermic	I	1B	221
	ECP	Non-erythrodermic	III	2C	
Dilated cardiomyopathy, idiopathic	IA	NYHA II-IV	II	1B	223
	TPE	NYHA II-IV	III	2C	
Erythropoietic protoporphyria, liver disease	TPE		III	2C	225
	RBC Exchange		III	2C	

(Continues)

TABLE 1 (Continued)

Disease	TA modality	Indication	Category	Grade	Page
Familial hypercholesterolemia	LA	Homozygotes	I	1A	227
	LA	Heterozygotes	II	1A	
	TPE	Homozygotes/ Heterozygotes	II	1B	
Focal segmental glomerulosclerosis (FSGS)	TPE/IA	Recurrent in kidney transplant	I	1B	229
	LA	Recurrent in kidney transplant/ Steroid resistant in native kidney	II	2C	
	TPE	Steroid resistant in native kidney	III	2C	
Graft-versus-host disease (GVHD)	ECP	Acute	II	1C	231
	ECP	Chronic	II	1B	
Hemolysis, elevated liver enzymes, and low platelets syndrome (HELLP Syndrome)	TPE	Postpartum	III	2C	233
	TPE	Antepartum	IV	2C	
Hemophagocytic lymphohistiocytosis (HLH); Hemophagocytic syndrome; Macrophage activating syndrome	TPE		III	2C	235
Heparin-induced thrombocytopenia and thrombosis (HIT/HITT)	TPE	Pre-cardiopulmonary bypass	III	2C	237
	TPE	Thrombosis	III	2C	
Hereditary hemochromatosis	Erythrocytapheresis		I	1B	239
Hyperleukocytosis	Leukocytapheresis	Symptomatic	II	2B	241
	Leukocytapheresis	Prophylactic or secondary	III	2C	
Hypertriglyceridemic pancreatitis	TPE/LA	Severe	III	1C	243
	TPE/LA	Prevention of relapse	III	2C	
Hyperviscosity in hypergammaglobulinemia	TPE	Symptomatic	I	1B	245
	TPE	Prophylaxis for rituximab	I	1C	
IgA nephropathy (Berger's Disease)	TPE	Crescentic	III	2B	247
	TPE	Chronic progressive	III	2C	
Immune thrombocytopenia (ITP)	TPE/IA	Refractory	III	2C	249
Inflammatory bowel disease	Adsorptive cytapheresis	Ulcerative colitis/Crohn's disease	III	1B	251
	ECP	Crohn's disease	III	2C	
Lambert-Eaton myasthenic syndrome	TPE		II	2C	253
Lipoprotein(a) hyperlipoproteinemia	LA	Progressive atherosclerotic cardiovascular disease	II	1B	255
Malaria	RBC Exchange	Severe	III	2B	257
Multiple sclerosis	TPE	Acute attack/relapse	II	1A	259
	IA	Acute attack/relapse	II	1B	
	TPE	Chronic	III	2B	
	IA	Chronic	III	2B	

(Continues)

TABLE 1 (Continued)

Disease	TA modality	Indication	Category	Grade	Page
Myasthenia gravis	TPE/IA	Acute, short-term treatment	I	1B	261
	TPE/IA	Long-term treatment	II	2B	
Myeloma cast nephropathy	TPE		II	2B	263
Nephrogenic systemic fibrosis	ECP/TPE		III	2C	265
Neuromyelitis optica spectrum disorders (NMOSD)	TPE	Acute attack/relapse	II	1B	267
	IA	Acute attack/relapse	II	1C	
	TPE	Maintenance	III	2C	
N-methyl-D-aspartate receptor antibody encephalitis	TPE/IA		I	1C	269
Overdose, envenomation, and poisoning	TPE	Mushroom poisoning	II	2C	271
	TPE	Envenomation	III	2C	
	TPE	Drug overdose/poisoning	III	2C	
Paraneoplastic neurological syndromes	TPE/IA		III	2C	273
Paraproteinemic demyelinating neuropathies; Chronic acquired demyelinating polyneuropathies	TPE	IgG/IgA/IgM	I	1B	275
	TPE	Anti-MAG neuropathy	III	1C	
	TPE	Multiple myeloma	III	2C	
	TPE	Multifocal motor neuropathy	IV	1C	
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS); Sydenham's chorea	TPE	PANDAS, exacerbation	II	1B	277
	TPE	Sydenham's chorea, severe	III	2B	
Pemphigus vulgaris	TPE	Severe	III	2B	279
	ECP/IA	Severe	III	2C	
Peripheral vascular diseases	LA		II	1B	281
Phytanic acid storage disease (Refsum's Disease)	TPE/LA		II	2C	283
Polycythemia vera; Erythrocytosis	Erythrocytapheresis	Polycythemia vera	I	1B	285
	Erythrocytapheresis	Secondary erythrocytosis	III	1C	
Post-transfusion purpura (PTP)	TPE		III	2C	287
Progressive multifocal leukoencephalopathy (PML) associated with natalizumab	TPE		III	1C	289
Pruritus due to hepatobiliary diseases	TPE	Treatment resistant	III	1C	291
Psoriasis	ECP	Disseminated pustular	III	2B	293
	Adsorptive cytapheresis	Disseminated pustular	III	2C	
	TPE	Disseminated pustular	IV	2C	
Red cell alloimmunization, prevention and treatment	RBC exchange	Exposure to RhD+ RBCs	III	2C	295
	TPE	Pregnancy, GA < 20 wks	III	2C	
Scleroderma (Systemic sclerosis)	TPE		III	2C	297
	ECP		III	2A	

(Continues)

TABLE 1 (Continued)

Disease	TA modality	Indication	Category	Grade	Page
Sepsis with multiorgan failure	TPE		III	2B	299
Sickle cell disease, acute	RBC exchange	Acute stroke	I	1C	301
	RBC exchange	Acute chest syndrome, severe	II	1C	
	RBC exchange	Other complications	III	2C	
Sickle cell disease, non-acute	RBC exchange	Stroke prophylaxis	I	1A	303
	RBC exchange	Pregnancy	II	2B	
	RBC exchange	Recurrent vaso-occlusive pain crisis	II	2B	
	RBC exchange	Pre-operative management	III	2A	
Steroid-responsive encephalopathy associated with autoimmune thyroiditis (Hashimoto's encephalopathy)	TPE		II	2C	305
Stiff-person syndrome	TPE		III	2C	307
Sudden sensorineural hearing loss	LA/Rheopheresis/TPE		III	2A	309
Systemic lupus erythematosus (SLE)	TPE	Severe complications	II	2C	311
Thrombocytosis	Thrombocytapheresis	Symptomatic	II	2C	313
	Thrombocytapheresis	Prophylactic or secondary	III	2C	
Thrombotic microangiopathy, coagulation mediated	TPE	*THBD*, *DGKE*, and *PLG* mutations	III	2C	315
Thrombotic microangiopathy, complement mediated	TPE	Factor H autoantibody	I	2C	317
	TPE	Complement factor gene mutations	III	2C	
Thrombotic microangiopathy, drug associated	TPE	Ticlopidine	I	2B	319
	TPE	Clopidogrel	III	2B	
	TPE	Gemcitabine/Quinine	IV	2C	
Thrombotic microangiopathy, infection associated	TPE/IA	STEC-HUS, severe	III	2C	321
	TPE	pHUS	III	2C	
Thrombotic microangiopathy, thrombotic thrombocytopenic purpura (TTP)	TPE		I	1A	323
Thrombotic microangiopathy, transplantation associated	TPE		III	2C	325
Thyroid storm	TPE		II	2C	327
Toxic epidermal necrolysis (TEN)	TPE	Refractory	III	2B	329
Transplantation, cardiac	ECP	Cellular/recurrent rejection	II	1B	331
	ECP	Rejection prophylaxis	II	2A	
	TPE	Desensitization	II	1C	
	TPE	Antibody mediated rejection	III	2C	

(Continues)

TABLE 1 (Continued)

Disease	TA modality	Indication	Category	Grade	Page
Transplantation, hematopoietic stem cell, ABO incompatible (ABOi)	TPE	Major ABOi HPC(M)	II	1B	333
	TPE	Major ABOi HPC(A)	II	2B	
	RBC Exchange	Minor ABOi HPC(A)	III	2C	
	TPE	Major/Minor ABOi w/ pure RBC aplasia	III	2C	
Transplantation, hematopoietic stem cell, HLA desensitization	TPE		III	2C	335
Transplantation, liver	TPE	Desensitization, ABOi living donor	I	1C	337
	TPE	Desensitization, ABOi deceased donor/ Antibody mediated rejection	III	2C	
	ECP	Desensitization, ABOi	III	2C	
	ECP	Acute rejection/Immune suppression withdrawal	III	2B	
Transplantation, lung	ECP	Bronchiolitis obliterans syndrome	II	1C	339
	TPE	Antibody mediated rejection/desensitization	III	2C	
Transplantation, renal, ABO compatible	TPE/IA	Antibody mediated rejection	I	1B	341
	TPE/IA	Desensitization, living donor	I	1B	
	TPE/IA	Desensitization, deceased donor	III	2C	
Transplantation, renal, ABO incompatible	TPE/IA	Desensitization, living donor	I	1B	343
	TPE/IA	Antibody mediated rejection	II	1B	
Vasculitis, ANCA-associated (AAV)	TPE	MPA/GPA/RLV: RPGN, Cr ≥ 5.7	I	1A	345
	TPE	MPA/GPA/RLV: RPGN, Cr < 5.7	III	2C	
	TPE	MPA/GPA/RLV: DAH	I	1C	
	TPE	EGPA	III	2C	
Vasculitis, IgA (Henoch-Schönlein purpura)	TPE	Crescentic RPGN	III	2C	347
	TPE	Severe extrarenal manifestations	III	2C	
Vasculitis, other	TPE	Hepatitis B polyarteritis nodosa	II	2C	349
	TPE	Idiopathic polyarteritis nodosa	IV	1B	
	Adsorptive cytapheresis	Behcet's disease	II	1C	
	TPE	Behcet's disease	III	2C	
Voltage-gated potassium channel (VGKC) antibody related diseases	TPE/IA		II	1B	351
Wilson disease, fulminant	TPE		I	1C	353

TABLE 2 Category Definitions for Therapeutic Apheresis

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
III	Optimum role of apheresis therapy is not established. Decision making should be individualized.
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.

IRB = Institutional Review Board

has been incorporated into the "Transplantation, hematopoietic stem cell, ABO incompatible" fact sheet. The "Hashimoto's encephalopathy" fact sheet has been renamed "Steroid-responsive encephalopathy associated with autoimmune thyroiditis (Hashimoto's encephalopathy)." The "Immunoglobulin A nephropathy" has been renamed "IgA nephropathy (Berger's Disease)." The "Thrombotic thrombocytopenic purpura" fact sheet has been renamed "Thrombotic microangiopathy, thrombotic thrombocytopenic purpura." The "Red cell alloimmunization in pregnancy" fact sheet was combined with "Prevention of RhD alloimmunization after RBC exposure" and renamed "Red cell alloimmunization, prevention and treatment." The Dermatomyositis/polymyositis fact sheet was retired. The total number of diseases and indications addressed in the Eighth Edition are 84 and 157, respectively. Distribution by category and grade is shown in Figure 3.

2 | METHODOLOGY

2.1 | Evidence-Based Approach

The JCA Special Issue 2007 (Fourth Edition) incorporated evidence-based medicine into well-defined and widely accepted ASFA Categories and quality of the evidence (Szczepiorkowski, 2007). In the JCA Special Issue 2010 (Fifth Edition), this system was modified to revise category definitions, maintain quality of the evidence, and add strength of the recommendation (Szczepiorkowski, 2010). In the JCA Special Issue 2013 (Sixth Edition), this was further refined

TABLE 3 Grading Recommendations, Strength and Quality of Evidence

Recommendation	Description	Methodological Quality of Supporting Evidence	Implications
Grade 1A	Strong recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1B	Strong recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1C	Strong recommendation, low-quality or very low- quality evidence	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
Grade 2A	Weak recommendation, high quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2B	Weak recommendation, moderate-quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

RCT = Randomized controlled trial
Adopted from Guyatt, 2006; 2008.

TABLE 4 Therapeutic Apheresis Modality Definitions

Procedure/term	Definition
Adsorptive cytapheresis	A therapeutic procedure in which blood of the patient is passed through a medical device, which contains a column or filter that selectively adsorbs activated monocytes and granulocytes, allowing the remaining leukocytes and other blood components to be returned to the patient.
ß$_2$-microglobulin column	A therapeutic apheresis procedure that uses a column containing porous cellulose beads specifically designed to bind to ß2-microglobulin as the patient's blood passes over the beads.
Double filtration plasmapheresis (DFPP)	A filter based therapeutic procedure that removes pathogenic substances from separated plasma based on their size, which is mainly determined by molecular weight and three-dimensional configuration (e.g., autoantibodies, immune complexes, lipoproteins, etc.), by using plasma filters with different pore sizes.
Erythrocytapheresis	A procedure in which blood of the patient or donor is passed through a medical device which separates red blood cells from other components of blood. The red blood cells are removed and replaced with crystalloid or colloid solution, when necessary.
Extracorporeal photopheresis (ECP)	A therapeutic procedure in which the buffy coat is separated from the patient's blood, treated extracorporeally with a photoactive compound (e.g., psoralens) and exposed to ultraviolet A light then subsequently reinfused to the patient during the same procedure.
Immunoadsorption (IA)	A therapeutic procedure in which plasma of the patient, after membrane based or centrifugal separation from the blood, is passed through a medical device (adsorber column) which has a capacity to remove immunoglobulins by binding them to select ligands on the backing matrix surface (membranes or beads) of the adsorber column.
Leukocytapheresis	A procedure in which blood of the patient is passed through a medical device which separates out white blood cells (e.g., leukemic blasts or granulocytes), collects the selected cells and returns the remainder of the patient's blood with or without addition of replacement fluid such as colloid and/or crystalloid solution.
Lipoprotein apheresis (LA)	The selective removal of lipoprotein particles from the blood with the return of the remaining components. A variety of methodologies are available and include double filtration plasmapheresis (DFPP), HELP-apheresis, polyclonal-sheep-anti-apoB-immunoadsorption, dextran-sulfate plasma adsorption, dextran-sulfate whole blood adsorption, and polyacrylate whole blood adsorption.
RBC exchange	A therapeutic procedure in which blood of the patient is passed through a medical device which separates red blood cells from other components of blood. The patient's red blood cells are removed and replaced with donor red blood cells and colloid solution.
Rheopheresis	A therapeutic procedure in which blood of the patient is passed through a medical device which separates out high-molecular weight plasma components such as fibrinogen, α2-macroglobulin, low-density lipoprotein cholesterol, and IgM in order to reduce plasma viscosity and red cell aggregation. This is done to improve blood flow and tissue oxygenation. LA devices and selective filtration devices utilizing two filters, one to separate plasma from cells and a second to separate the high-molecular weight components, are used for these procedures.
Therapeutic plasma exchange (TPE)	A therapeutic procedure in which blood of the patient is passed through a medical device which separates out plasma from other components of blood. The plasma is removed and replaced with a replacement solution such as colloid solution (e.g., albumin and/or plasma) or a combination of crystalloid/colloid solution.
Thrombocytapheresis	A therapeutic procedure in which blood of the patient is passed through a medical device which separates out platelets, removes the platelets and returns the remainder of the patient's blood with or without addition of replacement fluid such as colloid and/or crystalloid solution.

to provide information on categorization, and strength of recommendation based on the GRADE system (Guyatt 2006; 2008), which takes methodological quality of supporting evidence into account, while eliminating the need for "Level of Evidence" information used in previous fact sheets (Schwartz, 2013). The current edition follows the format used in the Sixth and Seventh Editions (Schwartz, 2016) and provides information on ASFA category (Table 2), and quality of supporting evidence that forms the basis of the grading recommendation (Table 3).

2.2 | ASFA Categories

The definition of the four ASFA categories in the Eighth Edition remains unchanged from the definition used in the Sixth and Seventh Editions (Table 2). This allowed us to

TABLE 5 Category IV Recommendations for Therapeutic Apheresis*

Disease	Procedure	Full Fact Sheet in JCA Special Edition
Amyotrophic lateral sclerosis	TPE	2013
Dermatomyositis/ polymyositis	TPE, ECP	2016
Inclusion body myositis	TPE, Leukocytapheresis	2013
POEMS syndrome	TPE	2013
Rheumatoid arthritis	TPE	2010
Schizophrenia	TPE	2013

*This table summarizes diseases where published evidence demonstrates or suggests apheresis to be ineffective or harmful (i.e., Category IV). This table excludes diseases in which apheresis may be ineffective in some settings, but may potentially be used in other settings in the same disease (e.g., HELLP syndrome: category III postpartum; category IV antepartum) or where one type of apheresis may be ineffective, while a different apheresis modality may potentially be useful in the same disease (e.g., TPE vs. ECP or adsorptive cytapheresis in Psoriasis).

maintain a consistent approach to categorize disease states and provide a grading recommendation, which incorporates the quality of published evidence in the literature.

2.3 | Grade of Recommendation

The Writing Committee recognizes the challenges in assessing study quality and translating recommendations into clinical practice. In the Fifth, Sixth and Seventh Editions, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to assign recommendation grades for TA to enhance the clinical value of ASFA categories (Guyatt 2006; 2008). We have continued this approach in the Eighth Edition (Table 3). It is important to note that the grade can be used in support or against the use of the therapeutic intervention. In addition, previously designated weak recommendations for diseases/conditions, such as Grade 2C, are more likely to be affected by additional evidence of higher quality than diseases that already have strong recommendations (e.g., Grade 1A). A number of factors can affect the quality of published evidence. As an example, the quality of evidence based on a RCT can be significantly diminished by poor quality of planning and implementation suggesting a high likelihood of bias, inconsistency of results, indirectness of evidence, and/or sparse outcome data. The members of the committee carefully took these variables into consideration while categorizing and grading diseases, TA modalities and/or indications.

2.4 | Design of the Fact Sheet

The 2019 JCA Special Issue Writing Committee made no changes in the design of the fact sheet from the Seventh Edition based on continued positive feedback regarding the fact sheet format. The information, provided in this format is comprehensive but limited in length to facilitate its use as a quick reference. The design of the fact sheet and explanation of information contained is included in Figure 1. The authors encourage the reader to use this figure as a guide to interpretation of all entries in the fact sheets as substantial condensing of available information was required to achieve this user-friendly format. References are limited to 20 and are not meant to be exhaustive but rather serve as a starting point in a search for more information.

2.5 | ASFA Category Assignments for 2019

The process for ASFA category assignment developed for previous editions continues to be maintained and enhanced by stringent application of evidence-based criteria to ensure consistency within and across fact sheets. The JCA Special Issue Writing Committees strive to be comprehensive and systematic in assembling objective evidence for disease indications, with strength of recommendation based upon the quality of the evidence. The 2019 JCA Special Issue Writing Committee, consisting of 13 ASFA members, was established in 2017. This group reviewed, revised, and amended indications for the use of TA in a very wide range of diseases. The membership of ASFA was also queried for new indications for apheresis therapy that had not previously been categorized by the JCA Special Issue Writing Committee.

The process of developing new and amending old fact sheets consisted of four steps (Figure 2). **Step I** created a list of fact sheets to be included. **Step II** assigned each of the working group members up to 10 diseases each to review. At a minimum, the review consisted of identifying all articles published in the English language, which described the use of TA in the disease or condition. For suggested new fact sheets, one or more committee members evaluated the available literature for evidence for the use of TA in the disease or condition. To meet criteria for a new fact sheet, the committee required a minimum of 10 cases published in the last decade in peer-reviewed journals, ideally by more than one group. All diseases or conditions considered for new fact sheet development were deemed to currently have inadequate information to assign fact sheets in this edition. These may be considered in future editions as new evidence emerges (Table 6). **Step III** consisted of circulating the first draft (draft I) of the fact sheet to two other members of the committee for critique and comment. In some cases, draft I was also sent to external subject matter experts for comments (see Acknowledgment section below). Based on these

comments, the author created draft II. In **Step IV**, all fact sheets were discussed and then finalized by consensus. Each disease, TA modality, and indication was assigned an ASFA category and grade of recommendation by consensus at a face-to-face meeting and/or conference calls. Members of the committee were encouraged to use "McLeod's Criteria" (McLeod, 2002) to assess the indication for which apheresis treatment was being evaluated for efficacy. We encourage practitioners of apheresis medicine to use these criteria when considering the use of TA in rare medical conditions, which may yet to be categorized by JCA Special Issue Writing Committee.

ASFA category and grade of recommendation for 84 diseases or conditions are summarized in Table 1. Unlike the 2016 JCA Special Issue, in this edition if more than one type of apheresis modality was used for the same clinical indication within the same disease or condition, and if the assigned recommendation grade and category were identical for each modality, it was assigned as a single indication. As an example, "Nephrogenic systemic fibrosis" is Category III and Grade 2C for both ECP and TPE modalities and is now classified as one indication. As a result, the number of indications is fewer than in the JCA 2016 Special Issue. However, in keeping with the Seventh Edition, if TA was used in more than one indication in the same disease or condition, each indication was assigned a recommendation grade and category. As an example, the "Transplantation, lung" fact sheet includes three different indications: desensitization,

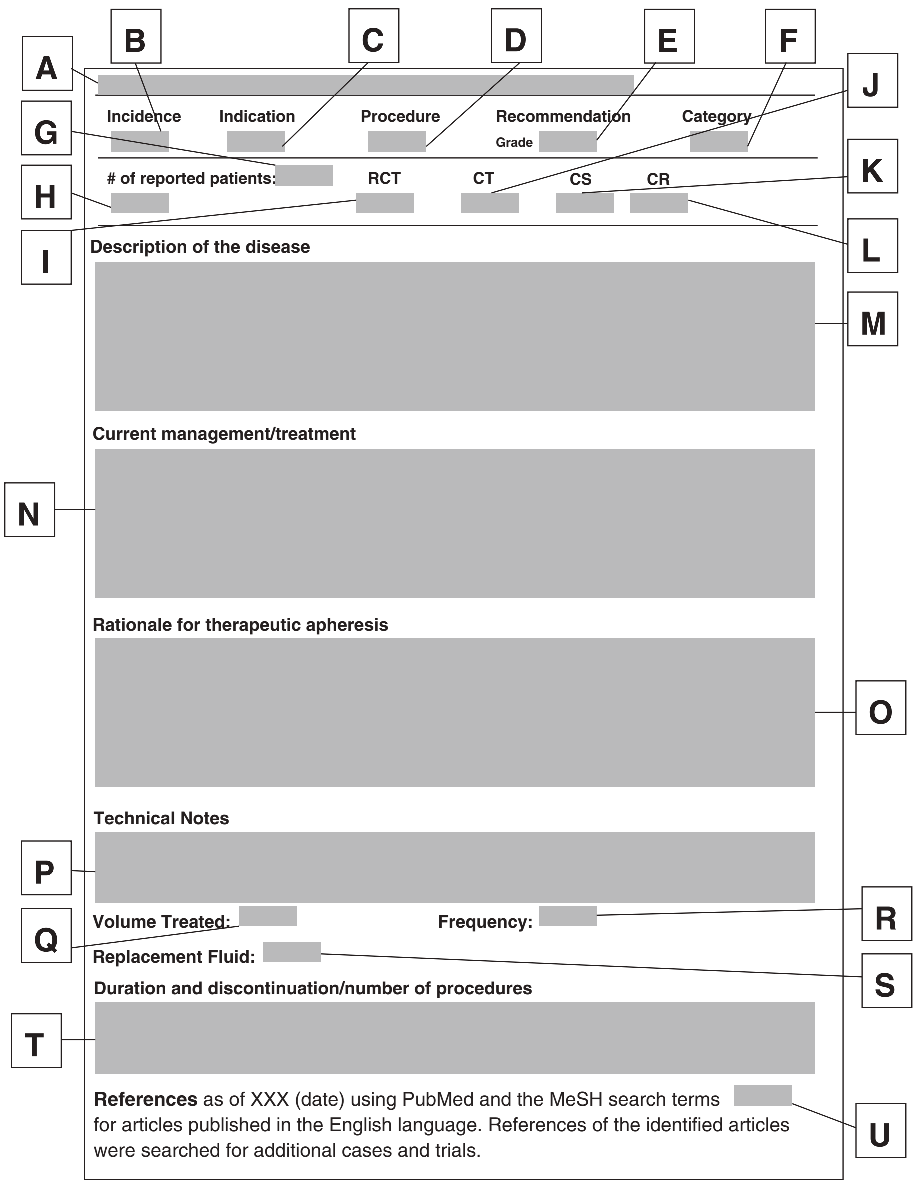


FIGURE 1 Legend on next page.

antibody mediated rejection, and bronchiolitis obliterans syndrome. Desensitization and antibody mediated rejection are combined because they have the same category and grade. Providing this level of detail in the fact sheet is expected to provide adequate clinical practice information to assist in appropriate management patients with complex conditions.

FIGURE 1 **A.** The name of the disease as well as its eponym or common abbreviation when appropriate. **B.** This section lists the incidence or prevalence of the disease in the US and other selected geographic regions, when appropriate. In some instances, when the incidence varies between genders, ethnicity, age, or race, this information is noted as well. For certain diseases with insufficient data on incidence or prevalence, other terms, such as rare or unknown are used. The reader is cautioned to use this information only as a general indicator of disease incidence or prevalence. For some diseases, this may vary by geographical area. **C.** The indication section refers to the use of apheresis in specific situations encountered in the disease (e.g. antibody mediated rejection [indication] in the setting of Transplantation, cardiac [disease]). **D.** The type of therapeutic apheresis procedure is listed here. For certain diseases there are several apheresis based modalities available. In such instances, more than one type of therapeutic apheresis modality is listed (e.g., Transplantation, lung). **E.** Recommendation grade is assigned to each categorized entity. As noted in the text the authors used the Grading of Recommendations Assessment Development and Evaluation (GRADE) system for grading the level of clinical recommendation. **F.** The ASFA category is listed for each therapeutic apheresis modality discussed. **G.** This section lists the number of patients reported in the literature who were treated with therapeutic apheresis. The committee used three categories: fewer than 100, between 100 and 300, and more than 300. This entry will help readers in judging how often this entity was reported to be treated with therapeutic apheresis. However, the number of patients treated is often less important than the quality of the scientific reports. **H.** This section is used when there are several different therapeutic apheresis procedures used and it was necessary to subdivide available scientific reports, as well as in the situation when different subsets of patients are being analyzed. Not all entries will have this section. **I.** Randomized controlled trials (RCT). The number of RCTs and the total number of patients studied. For example, 4(250) indicates that there were four RCTs with 250 enrolled patients. The patient count includes all patients irrespective of randomization to either treatment group (with therapeutic apheresis) or the control arm. The minimum requirement for these studies was randomization to a control arm and a test arm. The quality of the study is not reflected here. Example: Two randomized studies with 50 patients in each of two arms and one randomized study with 75 patients in each of two arms is denoted as 3(350). Patient counts should be not regarded as exact figures of all existing literature, but reflecting the magnitude of published evidence for a particular indication, and representing the major source of evidence used to assign category and grade recommendation. **J.** Controlled trials (CT): the notation is similar to RCTs. Studies listed here were not randomized. The control group could be historical or concurrent to the treatment group. Patient counts should be not regarded as exact figures of all existing literature, but reflecting the magnitude of published evidence for a particular indication, and representing the major source of evidence used to assign category and grade recommendation. **K.** Case series (CS). Number of case series (with total number of patients reported). If there were a significant number of patients in larger studies, NA (not applicable) was used. We required that the case series described at least three patients. Case series with two patients were included in case reports. Example: 4(56) implies that there were four case series with the total number of 56 reported patients. Patient counts should be not regarded as exact figures of all existing literature, but reflecting the magnitude of published evidence for a particular indication, and representing the major source of evidence used to assign category and grade recommendation. **L.** Case report (CR). Number of case reports (with total number of patients reported). If there were a significant number of patients in larger studies, NA (not applicable) was used. Patient counts should be not regarded as exact figures of all existing literature, but reflecting the magnitude of published evidence for a particular indication, and representing the major source of evidence used to assign category and grade recommendation. **M.** A brief description of the disease is provided here. Typically, this entry contains information on clinical signs and symptoms, pathophysiology, presentation and the severity of the disease. **N.** This section provides a brief description of therapeutic modalities available to treat the disease. The committee attempted to cover all reasonable modalities (e.g., medications, surgical procedures, etc.); however, this section is not intended to provide extensive discussion of any specific treatment modality. In addition, for some entities the management of standard therapy failure is discussed (e.g. steroids), especially when the failure of established therapies may trigger the use of therapeutic apheresis. **O.** This section discusses a rationale for therapeutic apheresis use in the disease and summarizes the evidence in this area. **P.** This section briefly describes technical suggestions relevant to the treated disease, which the committee believed were important to improve quality of care or increase chances of a positive clinical outcome. Not all diseases may have specific technical notes; in such instances, a general statement referring to the introductory text is provided. **Q.** This section specifies commonly used volumes of plasma or blood treated. **R.** The proposed frequency of treatment is listed here. The frequency reported was typically based on data from published reports. However, in some settings, due to significant variability in treatment schedules reported by different groups, the committee suggested what is believed to be the clinically most appropriate frequency. Application of this information may vary depending on the patient and clinical presentation, and is left to the discretion to the treating physician. **S.** The type of replacement fluid most frequently used is listed here. Terms such as plasma or albumin were used to denote the type of replacement fluid. No attempt was made to include all possible variations (e.g., 4% vs. 5% albumin; fresh frozen plasma vs. thawed plasma vs. solvent detergent plasma vs. cryoprecipitate-poor plasma). In addition, blood component modifications are listed here, if relevant (e.g., RBC modifications for red cell exchange). 'NA' is used when there is no replacement fluid necessary (e.g., extracorporeal photopheresis). **T.** This section provides basic criteria for discontinuation of apheresis procedures (i.e., end points/outcomes, both clinical and laboratory). In some instances, the number of procedures/series which may be reasonably employed in the particular clinical situation is suggested based upon currently available data. The committee believes that a thoughtful approach to patient management is required to establish reasonable and scientifically sound criteria for discontinuation of treatment. **U.** The terms used to identify relevant articles are listed here.

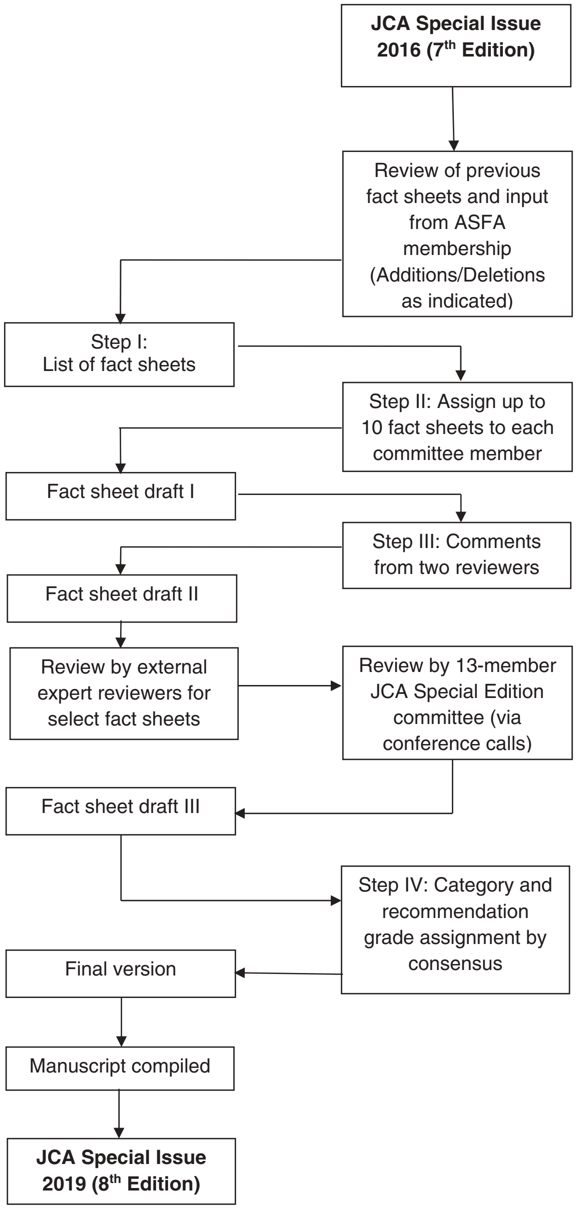


FIGURE 2 Systematic approach to ASFA category and recommendation grade assignment, fact sheet generation and revision in the 2019 Special Issue

The frequency of ASFA categories and recommendation grades is illustrated in Figure 3. As with previous editions, there is a significant expansion in the number of indications (relative to the number of diseases categorized) and is accounted for by some diseases having several categories and recommendation grades due to multiple indications within the same disease, or multiple apheresis modalities used to treat the same disease with different grade recommendations. In a minority of diseases, there was only a single indication, e.g., TPE in "Lambert-Eaton myasthenic syndrome." Thus, a total of 84 diseases and 157 indications are categorized (Figure 3). The number of category I, II, III and IV indications are 29, 43, 79, and 6, respectively (Table 1 and Figure 3). The majority of category I indications have recommendation grades of 1A-C. Category II indications are spread through the entire spectrum of recommendation grades with nearly half with recommendation grade 1A-C, and the remainder with recommendation grade 2A-C. As in prior editions, the majority (54/79=68%) of category III indications have recommendation grade 2C (weak recommendation with low/very low-quality evidence). The number of category IV indications include 6 listed in full fact sheets in this edition, and several additional diseases listed in Table 5 that cite previous JCA Special Editions containing full fact sheets.

TABLE 6 Diseases considered for new fact sheets in 2019

Disease
Alzheimer's disease
Antisynthetase syndrome
Autoimmune myofasciitis
Composite tissue transplantation
Fulminant meningococcemia
Mechanical red cell hemolysis
Methemoglobulinemia
Necrotizing myopathy
Pancreatic transplantation
Platelet transfusion allorefractoriness
Pre-eclampsia
Recurrent pregnancy loss

2.6 | General Considerations

The format of the Special Issue restricts the amount of information that can be provided in each fact sheet. For additional information, one textbook in the field of apheresis medicine which users of the Special Issue may find useful is Apheresis: Principles and Practice, Third Edition (McLeod, 2010). The recommendations of the ASFA "Choosing Wisely" campaign should also be considered when planning a procedure and informative communication between apheresis providers, prescribers, and patients is encouraged (Connelly-Smith, 2018). In Table 7, we propose information that may be included in a consultation note before performing an apheresis procedure. This standard approach to consultation may be particularly helpful to readers who may have limited experience in the field of apheresis medicine. An area of potential concern for the apheresis practitioner is type of replacement fluid to be used during therapeutic apheresis, notably TPE. The reader should be cognizant of the risk of coagulation factor depletion (especially fibrinogen), particularly after daily TPE used in some clinical settings. Coagulation factor

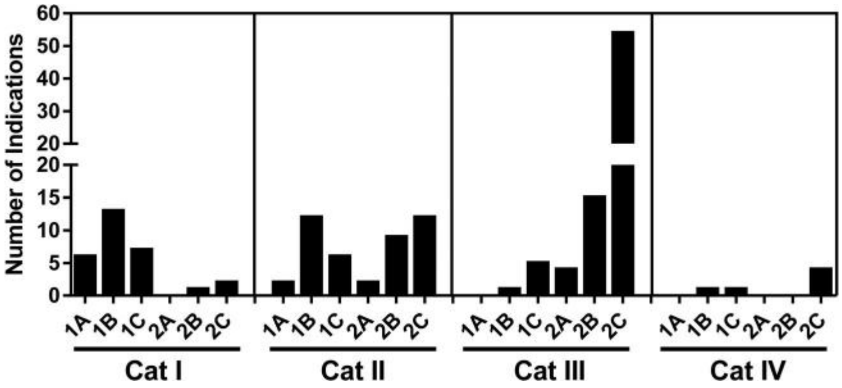


FIGURE 3 Category and recommendation distribution in the 2019 Special Issue

replacement (e.g., plasma or cryoprecipitate supplementation) may be considered in these situations.

Technical considerations regarding the use of ECP are not fully described in each of the individual fact sheets and prescribers should ensure familiarity with potential risks associated with the use of psoralen. For example, ECP should not be performed in patients with aphakia (absence of lens) due to increased risk for retinal damage and patients should be instructed to wear eye and skin protection for 24 hours following treatment due to increased photosensitivity from the psoralen infused with the buffy coat. There may be a risk of venous thromboembolism in patients receiving ECP, as noted in a 2018 MedWatch Safety Alert issued by the U.S. Food and Drug Administration (FDA). The reasons for these observations are not fully understood but providers should inform their patients of the potential risk while receiving treatment with ECP. Finally, there has recently been a technical bulletin released adding splenectomy as a contraindication to performing ECP.

Issues related to the timing of procedures, such as emergency (treatment indicated within hours), urgent (within a day), and routine, are not addressed directly in the fact sheets given the heterogeneity of patient disease presentation. The patient's clinical condition and diagnosis, as well as availability of alternative therapies, should be carefully evaluated when determining the optimal timing and duration of apheresis therapy. This determination should be made using appropriate medical judgment through consultation between the requesting physician and the physician administering apheresis. The 2019 JCA Special Issue should provide useful information to inform practitioners about the evidence-based application of TA for a wide range of disease states.

2.7 | Additional Information

2.7.1 | Immunoadsorption systems

Immunoadsorption (IA) has the capacity to remove immunoglobulins by binding them to select ligands on the backing matrix surface (membranes or beads) of the adsorber column. A major advantage of IA compared to TPE is that no substitution of human plasma products is necessary. In some

TABLE 7 General Issues to Consider When Evaluating a New Patient for Therapeutic Apheresis

General	Description
Rationale*	Based on the established/presumptive diagnosis and history of present illness, the discussion could include the rationale for the procedure, brief account of the results of published studies, and patient-specific risks from the procedure.
Impact	The effect of therapeutic apheresis on co-morbidities and medications (and vice-versa) should be considered.
Technical issues*	The technical aspects of therapeutic apheresis such as a type of anticoagulant, replacement solution, vascular access, and volume of whole blood processed (e.g., number of plasma volumes exchanged) should be addressed.
Therapeutic plan*	Total number and/or frequency of therapeutic apheresis procedures should be addressed.
Clinical and/or laboratory end-points*	The clinical and/or laboratory parameters should be established to monitor effectiveness of the treatment. The criteria for discontinuation of therapeutic apheresis should be discussed whenever appropriate.
Timing and location	The acceptable timing of initiation of therapeutic apheresis should be considered based on clinical considerations (e.g., medical emergency, urgent, routine etc.). The location where the therapeutic apheresis will take place should be also addressed (e.g., intensive care unit, medical word, operating room, outpatient setting). If the timing appropriate to the clinical condition and urgency level cannot be met, a transfer to a different facility should be considered based on the clinical status of the patient.

The above issues should be considered and explicitly discussed in a clinical note documenting the patient history, review of systems, and physical examination.
*ASFA fact sheet for each disease may be helpful in addressing these issues.

adsorbers however, monitoring of fibrinogen is recommended in cases where treatments are performed daily. In general, plasma product related risks of intolerability, transmission of infectious agents, or compromise of the coagulation system can be avoided with IA.

IA adsorbers can be subdivided into non-regenerative and regenerative columns. Non-regenerative columns are single use adsorbers limited to the treatment of approximately one patient's plasma volume and have their main indication in acute situations of autoantibody-mediated diseases. Regenerative adsorber systems consist of column pairs, which are sequentially regenerated during a treatment session, and may be reusable. They can treat up to three patient's plasma volumes in a single session. These systems are favorable if antibodies must be reduced to low threshold titers, such as that required for the conditioning of kidney transplant recipients with ABO-incompatibility or HLA-sensitization.

Most IA columns are broadband immunoglobulin adsorbers using different ligands (e.g., staphylococcal or recombinant protein A, sheep polyclonal anti-human antibodies, tryptophan, synthetic oligopeptides, monoclonal camel antibody fragments) to bind all major immunoglobulin subclasses. Specific antibody columns exist for ABO-blood group antigens (carbohydrate ligands) or IgE (monoclonal mouse antibodies). The level of experience with these different IA systems is very variable. If available, major publications can be found as references in individual fact sheets.

The use of IA systems in routine care is not universal due to the different regulatory status of medical device approval and the economic resources of health care systems. All systems are cleared by European authorities without strict disease limitations, a fundamental principle of FDA clearance. Manufacturing of the only IA system approved by the FDA in 1987 for immune thrombocytopenia (ITP), and in 1999 for refractory rheumatoid arthritis patients (i.e., staphylococcal protein A on silica) was discontinued in 2006, because the product never became implemented in routine care. The situation is heterogeneous in Asian countries. Even if regulatory approval exists country-specific regulations of reimbursement for apheresis treatments as part of outpatient or in-hospital care may additionally limit the actual use.

2.7.2 | Lipoprotein Apheresis systems

Six systems for selective lipoprotein apheresis (LA) are available, which in general use membrane plasma separation as the first step, if plasma is treated. These include:

1. Adsorption columns containing matrix-bound sheep anti-apo-B antibodies; due to this methodological characteristic the term immunoadsorption LA is used;
2. Dextran sulfate adsorption columns to remove apo-B containing lipoproteins from plasma by electrostatic interaction;
3. Heparin extracorporeal LDL precipitation (HELP) for selective precipitation of plasma proteins including the entire spectrum of atherogenic apo-B containing lipoproteins in the presence of heparin and low pH;
4. Direct adsorption of lipoproteins using hemoperfusion to remove apo-B containing lipoproteins from whole blood through electrostatic interactions with polyacrylate coated polyacrlyamide beads;
5. Dextran sulfate cellulose columns: same mechanism as (2) above but treats whole blood; and
6. Double filtration plasmapheresis (DFPP) for filtration of high-molecular weight apo-B containing atherogenic lipoproteins from plasma; the terms membrane differential filtration or cascade filtration are used synonymously in the literature; the term plasma filtration is used, if centrifugal plasma separation is the first step.

Currently, the dextran sulfate plasma adsorption and HELP apheresis systems are cleared by the FDA. According to scientific literature, all existing systems have equivalent reduction efficacy for LDL-cholesterol or lipoprotein(a), and there is no indication for differences in clinical outcome when used for long-term regular treatment. The fact sheets on "Familial hypercholesterolemia" and "Lipoprotein(a) hyperlipoproteinemia" provide information on LA as a whole without discussing each system separately.

2.7.3 | Rapidly Progressive Glomerulonephritis

A number of fact sheets in the 2019 JCA Special Issue discuss disease entities that may potentially present with the clinical syndrome of rapidly progressive glomerulonephritis (RPGN): "Amyloidosis, systemic," "Anti-glomerular basement membrane disease (Goodpasture syndrome)," "IgA nephropathy (Berger's Disease)," "Systemic lupus erythematosus (SLE)," "Vasculitis, ANCA-associated (AAV)," "Vasculitis, IgA (Henoch-Schönlein purpura)," and "Vasculitis, other."

RPGN is characterized by rapid loss of renal function (i.e. glomerular filtration rate) within days or weeks, with the clinical and histologic finding of glomerulonephritis. Overall, there is only a weak correlation of the underlying etiology with descriptive histologic patterns as detected by kidney biopsy. Many renal lesions encountered in RPGN can be present in several renal diseases. Glomerular, tubular, interstitial, and vascular lesions have to be separated. It

is not always clear which thresholds of histologic changes have clinical and prognostic value for a particular disease. Histologic lesion definitions and disease classification potentially guiding treatment decisions must be evaluated separately for every disease entity and are subject of ongoing scientific discussion.

In the decision-making process, light microscopy will be complemented by findings of immunofluorescence or electron microscopy to detect deposits of immunoglobulins, complement, or immune complexes. Pauci-immune glomerulonephritis is characterized by only mild or absent glomerular staining for immunoglobulin and complement and is typically seen with AAV. Extent of membranoproliferative patterns, crescents (i.e., lesions consisting of extracapillary hypercellularity, composed of a variable mixture of cells), fibrous crescents, segmental fibrinoid necrosis, interstitial fibrosis, or tubular atrophy reflect severe disease at the tissue level and predict worse prognosis.

The treatment of RPGN, which frequently requires interdisciplinary consultation, is usually based on the following: (1) diagnosis of the underlying etiology, (2) assessment of the clinical picture, and (3) evaluation of the kidney biopsy findings, if available. Diagnosis of the clinical syndrome of RPGN alone is not sufficient to determine the therapeutic strategy potentially including TA.

2.8 | Glossary

TA procedures considered in this publication and included in the fact sheets are defined in Table 4.

ACKNOWLEDGMENTS

Several fact sheets contained in this issue were reviewed by external experts (Figure 2). The 2019 JCA Special Issue Writing Committee is indebted to the following individuals for their contributions:

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ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)

Incidence: <1/100,000/yr*	Indication	Procedure	Recommendation	Category
	Steroid Refractory	TPE	Grade 2C	II
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	7(52)	29(35)

*In patients <20 years old. In adults, incidence estimates are not available.

Description of the disease

Acute disseminated encephalomyelitis (ADEM) is an acute inflammatory monophasic demyelinating disease that predominantly affects the white matter of the brain and spinal cord. It typically occurs after a viral or bacterial infection, or vaccination. ADEM may occur at any age but is most common during childhood with substantial differences in reported incidence between US, Europe or Asia. The pathogenesis is thought to be disseminated multifocal inflammation and patchy demyelination associated with transient autoimmune response against myelin oligodendrocyte glycoprotein or other autoantigens. It is believed that viral or bacterial epitopes resembling neuronal antigens have the capacity to activate myelin-reactive T cell clones through molecular mimicry, and thus can elicit a central nervous system (CNS) specific autoimmune response. ADEM typically begins within days to weeks presenting with an acute encephalopathy (change in mental status) accompanied by multifocal neurological deficits (ataxia, weakness, dysarthria, dysphagia, cranial nerve palsies, seizures, or fever). It is usually a monophasic illness with a favorable prognosis. Recurrent or multiphasic forms have been reported, particularly in children. The prognosis is favorable, with complete recovery within weeks or months in ~55-95% of cases while mortality is rare. Magnetic resonance imaging (MRI) is the diagnostic imaging modality of choice for the demyelinating lesions. Characteristic lesions seen on MRI appear as patchy areas of increased signal intensity with typical involvement of deep cerebral hemispheric and subcortical white matter, as well as lesions in the basal ganglia, gray-white junction, brain stem, cerebellum and spinal cord. The differentiation of ADEM from a first attack of multiple sclerosis (MS) has prognostic and therapeutic implications. ADEM has these features, which help to distinguish it from MS: florid polysymptomatic presentation, lack of oligoclonal bands in the cerebrospinal fluid, predominance of MRI lesions in the subcortical region with relative sparing of the periventricular area and complete or partial resolution of MRI lesions during convalescence. New lesions should not appear unless a clinical relapse has occurred. A rare hyperacute variant of ADEM, acute hemorrhagic leukoencephalitis, is characterized by a rapidly progressive, and fulminant hemorrhagic demyelination of white matter, usually associated with severe morbidity or death.

Current management/treatment

Once ADEM is diagnosed, the therapeutic aim is to abbreviate the CNS inflammatory reaction as quickly as possible, to aid in clinical recovery. There have been no RCTs for the treatment of ADEM, and therapies are based on the experience published in CRs or CS. Due to the postulated immune-mediated pathogenesis, treatment is based on immunomodulatory agents. The use of high-dose intravenous corticosteroids, such as methylprednisolone 20-30 mg/kg/day (maximum 1 gm/day) for 3-5 days, has been suggested on the basis of their efficacy in treating other demyelinating diseases such as MS, and is widely accepted now as first-line therapy. It may be followed by a prolonged oral prednisolone taper over 3-6 weeks. Corticosteroids are considered effective because of their anti-inflammatory and immunomodulatory effects with additional beneficial effect on cerebral edema. IVIG 2g/kg total dose, given over 2-5 days, is typically reserved for patients who are steroid unresponsive, but has also been rarely used as initial or concomitant therapy.

Rationale for therapeutic apheresis

TPE is thought to work by removing humoral determinants, in particular presumed pathogenic autoantibodies in ADEM. A potential candidate target of autoantibodies in ADEM is myelin oligodendrocyte glycoprotein. In one study, early initiation of TPE (within 15 days of disease onset) in acute attacks of CNS demyelination (including 7 cases of ADEM) was identified as a predictor of clinical improvement at 6 months (Llufriu, 2009). TPE should be considered as second-line therapy, alone or in conjunction with other therapeutic modalities, in patients with fulminant ADEM who respond poorly to steroid treatment and/or IVIG (Borras-Novell, 2015). In a large retrospective multicenter analysis of 228 ADEM patients, 17 patients (7%) required treatment escalation with TPE (Koelman, 2016). In this CS, either steroids, IVIG or both preceded TPE in all patients in whom it was used.

Technical notes

Volume treated: 1-1.5 TPV	**Frequency:** Every other day
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

There is no clear standard upon which to make recommendations on the optimal regimen of TPE in ADEM. The principal outcome of interest for therapeutic apheresis is acute response to treatment, rather than long-term effects on attack frequency. In one of the largest ADEM CS, TPE achieved moderate and marked sustained improvement in 40% of the patients (Keegan, 2002). Factors associated with improvement were male gender, preserved reflexes and early initiation of treatment. In most studies, clinical response was noticeable within days, usually after 2-3 exchanges. Most published experiences describe 5-7 treatments.

Keywords: ADEM, acute disseminated encephalomyelitis, inflammatory demyelinating disease, acute hemorrhagic leukoencephalitis

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ACUTE INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (GUILLAIN-BARRÉ SYNDROME)

Incidence: 1-2/100,000/yr	**Indication**	**Procedure**	**Recommendation**	**Category**
	Primary Treatment	TPE	Grade 1A	I
		IA	Grade 1B	I
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
TPE	21(1874)	0	NA	NA
IA	0	1(39)	6(105)	NA

Description of the disease

Guillain-Barré syndrome (GBS) is an acute, usually symmetrical, and typically ascending, paralyzing disorder caused by inflammation of the peripheral nerves. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP), which comprises up to 90% of GBS cases, is an acute progressive paralyzing illness affecting both motor and sensory peripheral nerves. The remainder of GBS cases are defined by presenting pathogenic and clinical features and classified as acute motor axonal neuropathy (AMAN), acute motor-sensory axonal neuropathy (AMSAN), Miller Fisher syndrome, and acute autonomic neuropathy. Weakness or sensory impairment progresses over a period of 12 hours to 28 days before nadir is reached and may involve respiratory and oropharyngeal muscles in severe cases. Thus, mechanical ventilation is required for ~25% of patients. Autonomic dysfunction can cause variability in blood pressure and heart rate resulting in life threatening complications. Spontaneous recovery may occur; however, neurologic complications persist in up to 20% of patients, with half severely disabled at 1 year. Mortality is estimated at 3-5%. Guillain-Barré syndrome is usually preceded by infection or other immune stimulation that induces an aberrant autoimmune response targeting peripheral nerves and their spinal roots. Molecular mimicry between microbial and nerve antigens is a major mechanism behind the development of the disorder, as suggested by the association with *Campylobacter jejuni* infection, and the increase of GBS incidence in regions with Zika virus outbreaks. However, how the immune response is shifted towards unwanted autoreactivity is still not well understood. Autoantibodies against various gangliosides, notably GM1 and GD1a, play a role, particularly in AMAN and Miller Fisher syndrome subtypes.

Current management/treatment

Since spontaneous recovery is anticipated in most patients, supportive care is the mainstay of treatment in ambulatory patients. Severely affected patients may require intensive care, mechanical ventilation, and assistance through paralysis and necessary rehabilitation over several months to a year or more. Corticosteroids are not beneficial in the disorder. In trials using TPE and/or IVIG in GBS, AIDP patients represented the majority compared to other variants. TPE was the first therapeutic modality to impact the disease favorably and several major RCTs have confirmed its efficacy. An international RCT compared TPE, IVIG and TPE followed by IVIG in 383 adult patients with severe AIDP and found all three modalities to be equivalent (Plasma Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group, 1997). There were no differences in the three treatment groups in mean disability improvement at 4 weeks nor the time to be able to walk without assistance (TPE group 49 days, IVIG group 51 days and TPE/IVIG group 40 days). IA avoids the need of replacing human plasma products and was used in one CT and several CS with similar efficacy as TPE. Other therapeutic modalities studied include cerebrospinal fluid filtration, double filtration plasmapheresis, and drug targeting of complement activation. Since IVIG is readily available and a more convenient form of immunomodulatory treatment, it is frequently used as initial therapy; the typical dose is 0.4 g/kg for 5 consecutive days.

Rationale for therapeutic apheresis

The favored pathogenesis of GBS is autoimmune antibody-mediated damage to peripheral nerve myelin. The results of several CTs comparing TPE to supportive care alone indicate that TPE can accelerate motor recovery, decrease time on the ventilator, and decrease time to attainment of other clinical milestones. While recovery with TPE is improved, the duration of disability from AIDP remains significant. The Cochrane Neuromuscular Disease Group review of TPE in AIDP performed in 2012 and updated in 2017 concluded that TPE is an effective treatment of GBS and should be initiated within 7 days of disease onset (Chevret, 2017). It was further concluded that TPE has beneficial effect in severely and mildly affected individuals; with significantly increased proportion of patients able to walk after 4 weeks. Furthermore, TPE was reported to be more cost effective in India than IVIG (Maheshwari, 2018). A priori combining of TPE and IVIG in sequential order was not advantageous and is not recommended. There are insufficient data to conclude on the efficacy of TPE after IVIG failure. Treatment decisions must be made on a case-by-case basis.

Technical notes

Since autonomic dysfunction may be present, affected patients may be more susceptible to intravascular volume shifts during apheresis treatments and should be monitored carefully. Relapses may occur in up to 5-10% of patients 2-3 weeks following either treatment with TPE or IVIG. When relapses occur, additional TPE is typically helpful.

Volume treated: TPE: 1-1.5 TPV; IA: up to 3 TPV	**Frequency:** Every other day or daily
Replacement fluid: TPE: Albumin or Plasma; IA: NA	

Duration and discontinuation/number of procedures

The typical TPE strategy is to exchange 1-1.5 plasma volumes 5-6 times over 10-14 days, some patients may need additional treatments. Considerations for IA are essentially identical.

Keywords: Acute inflammatory demyelinating polyradiculoneuropathy, GBS, Guillain-Barré syndrome

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ACUTE LIVER FAILURE

Incidence: <10/1,000,000/yr		**Procedure**	**Recommendation**	**Category**
		TPE-HV*	Grade 1A	I
		TPE	Grade 2B	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
TPE-HV	1(183)	0	0	NA
TPE	1(120)	1(158)	40(878)	NA

*TPE-HV = TPE-high volume, not in routine use in US

Description of the disease

Acute liver failure (ALF) can develop in a normal liver (known as fulminant hepatic failure [FHF]) or in the setting of chronic liver disease. The most common causes are acetaminophen toxicity and viral hepatitis. Other known causes include ingestion of hepatotoxins/drugs, autoimmune hepatitis, critical illness, neoplastic infiltration, acute Budd-Chiari syndrome, and heat stroke. The mortality rate in FHF is 50-90% due to acute metabolic disturbances, hepatic encephalopathy and severe coagulopathy; however, following liver transplantation (LT), survival rates improve. Spontaneous recovery from FHF depends on the cause: high recovery rates are observed in fatty liver of pregnancy, acetaminophen ingestion and hepatitis A; hepatitis B has intermediate prognosis; other drugs and unknown etiologies have a recovery rate of <20%.

Current management/treatment

For ALF with low likelihood of spontaneous recovery, the standard treatment is supportive care as a bridge to LT. If LT is not available, other liver support systems have been used but none has been shown conclusively to increase survival in this cohort of patients. Liver support systems include cell-based (bioartificial) and non-cell-based therapies. Many of the cell-based liver support systems have been in recent or current clinical trials (e.g., bioartificial liver, extracorporeal whole liver perfusion, extracorporeal liver assist device, and modular extracorporeal liver support). Non-cell-based therapies include TPE, albumin dialysis, molecular adsorbents recirculation system (MARS: in the US, the MARS system is FDA cleared for use in the treatment of drug overdose and poisonings only), fractionated plasma separation and adsorption, single pass albumin dialysis, and selective plasma-exchange therapy. Other newer promising approaches include hepatocyte transplantation and tissue engineering.

Rationale for therapeutic apheresis

In FHF, TPE can remove albumin bound toxins as well as unbound toxins, including aromatic amino acids, ammonia, endotoxin, indols, mercaptans, phenols and other factors which may be responsible for hepatic coma, hyperkinetic syndrome, and decreased systemic vascular resistance and cerebral blood flow. Studies indicate that the removal of inflammatory mediators appears to play a role in treatment of ALF and inflammatory mediators are removed by some apheresis techniques. Several studies show improved cerebral blood flow, mean arterial pressure (MAP), cerebral perfusion pressure, cerebral metabolic rate, increased hepatic blood flow, and improvements in other laboratory parameters such as cholinesterase activity or galactose elimination capacity. Despite these seemingly positive changes in physiological parameters, the impact of TPE on clinical improvement is still unclear. One study found that TPE does not reduce vasopressor requirement, despite positive changes in MAPs (Wiersema, 2015). TPE may also restore hemostasis by providing coagulation factors and removing activated clotting factors, tissue plasminogen activator, fibrin and fibrinogen degradation products. In some patients, the liver may recover during the period of TPE treatment and in other patients, failure may persist necessitating LT. Aggressive TPE has been used as a bridge to LT. When it is indicated, TPE is often performed emergently in this setting.

A RCT in ALF patients with hepatic encephalopathy showed that both MARS and TPE + MARS therapy are equivalent regarding clinical outcome (30-day mortality). However, TPE + MARS therapy reduced serum total bilirubin level more effectively (Huang, 2012). Similarly, the combined use of TPE, hemoperfusion (HP), and conventional continuous veno-venous hemofiltration removed toxic metabolites, especially bilirubin, more efficiently than other combinations without TPE (Li, 2014). A CT showed significant survival benefit in patients who received TPE versus those who did not for entecavir-treated hepatitis B and hepatic decompensation or acute-on-chronic liver failure (Wan, 2016). The cumulative survival rates were 37% (TPE) and 18% (non-TPE) at week 4 and 29% (TPE) and 14% (non-TPE) at week 12 ($p < 0.001$). In some centers in Denmark, Finland and UK, TPE-high volume (TPE-HV) has been used to treat ALF. An RCT performed in 183 patients demonstrated statistically significant liver transplant free survival benefit: 59% TPE-HV + standard care versus 48% standard care ($p < 0.001$) when 3 daily procedures were added to standard medical therapy in patients waiting for a liver transplant (Larsen, 2016). Unfortunately, however, TPE-HV prior to LT did not improve survival compared with patients who received standard medical therapy alone.

Technical notes

Since plasma has citrate as an anticoagulant and there is hepatic dysfunction, the whole blood: ACD-A ratio may need to be adjusted accordingly to prevent severe hypocalcemia. Alternatively, simultaneous calcium infusion can be used. Calcium supplementation should be strongly considered. Patients should also be monitored for development of metabolic alkalosis. Some groups have performed simultaneous hemodialysis to mitigate this side effect. There is a preference for plasma as a replacement fluid due to moderate to severe coagulopathy; however, use of albumin is acceptable.

Volume treated: TPE: 1-1.5 TPV; TPE-HV: target 8-12L exchange	**Frequency:** Daily
Replacement fluid: Plasma, albumin	

Duration and discontinuation/number of procedures

In ALF, daily TPE is performed until LT or self-regeneration occurs. The biochemical response to TPE should be evaluated in laboratory values drawn the following day (≥12 hours or more after TPE). Samples drawn immediately after completion of TPE would be expected to appear better compared to pre-TPE levels. TPE-HV was performed on 3 consecutive days.

Keywords: acute liver failure, fulminant liver/hepatic failure, high volume plasma exchange

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AGE RELATED MACULAR DEGENERATION, DRY

Prevalence: 2% (dry AMD and soft drusen, US population)	**Indication**	**Procedure**	**Recommendation**	**Category**
	High-risk	Rheopheresis	Grade 2B	II
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	6(433)	3(396)	NA	NA

AMD = age-related macular degeneration

Description of the disease

Age-related macular degeneration (AMD) is the leading cause of severe, irreversible vision impairment with progressive central vision loss among patients typically aged 50 years or older in developed countries. "Dry" (i.e., non-neovascular or atrophic) AMD is the most common form and is characterized by the accumulation of debris (drusen) which disrupt the functional complex of the retina (i.e., photoreceptors, retinal pigment epithelium [RPE], Bruch's membrane, and choriocapillaris) and may progress to geographic atrophy, or "wet" AMD, the most severe form of the disease, characterized by abnormal choroidal neovascularization. Although an estimated 80% of AMD patients have dry AMD, wet AMD is responsible for nearly 90% of severe vision loss. Treatment recommendations are based on a clinical classification to define early, intermediate, and late stages. Geographic atrophy of the fovea and neovascular maculopathy are always late stages. Cigarette smoking is the main modifiable risk factor. Genetic risk factors include mutations in complement factor H, cholesterol, collagen matrix and angiogenesis pathways. The pathogenesis of AMD has not been completely elucidated but senescence, characterized by lipofuscin accumulation in RPE cells, choroidal ischemia and oxidative damage may play a role.

Current management/treatment

Medical management of dry AMD is limited to oral supplements containing high doses of antioxidant vitamins, zinc, and copper. A variety of targeted therapies for dry AMD are in development, however, an approved active treatment approach for early, intermediate or progressive stages of dry AMD still does not exist. For wet AMD intravitreous anti-vascular endothelial growth factor injection has become first-line therapy. Photodynamic therapy and laser photocoagulation are used as second-line therapy.

Rationale for therapeutic apheresis

Rheopheresis removes rheologically active, high-molecular weight molecules (e.g., fibrinogen, LDL, α2-macroglobulin, fibronectin, von Willebrand factor) which may impair the retinal microcirculation or contribute to a chronic inflammatory state. Rheopheresis results in a reduction in blood and plasma viscosity, platelet and red cell aggregation, which may also improve RPE perfusion and function.

Multiple studies have reported efficacy of rheopheresis in the treatment of dry AMD. Additionally, data are available from 3 trials including case controls and several uncontrolled CS. One RCT studied 38 patients randomized to receive 8 procedures over 10 weeks and compared them to 34 untreated controls. Best-corrected visual acuity increased significantly from 0.61 (0.06-1.00) to 0.68 (0.35-1.00) in the treatment group ($p = 0.035$) (Blaha, 2013). The same group also noted significant reduction in the drusenoid RPE detachment area in a CT of 25 patients (Rencová, 2013). Both studies showed no progression to wet AMD in the treatment group during the 2.5-year follow-up period, suggesting that rheopheresis may slow or stop morphological progression of dry AMD.

The largest data set is from the RheoNet registry (Klingel, 2010). Four hundred twenty-eight eyes of 279 patients with dry AMD were treated and compared to 85 eyes of 55 untreated controls. In the treated group, visual acuity gain of ≥1 line on Early Treatment Diabetic Retinopathy Study (ETDRS) charts was seen in 42% compared to such improvement in 26% of controls after a mean observation period of 6.75 months. Vision loss ≥1 ETDRS line was seen in 17% of the treated patients versus 40% of controls. These were statistically significant differences.

The MIRA-1 trial, the largest RCT to date, enrolled 216 patients yet failed to demonstrate a significant difference between controls and treatment groups (Pulido, 2006). Analysis revealed that 37% of treated patients and 29% of control patients were protocol violators. Excluding those subjects in a per protocol analysis, this trial demonstrated significant improvement with treatment, but the trial was under-powered for FDA licensure.

Criticism of current evidence supporting the use of rheopheresis for treatment of dry AMD include the hypothetical mechanism of action by which the apheresis procedure improves RPE function, uncertainty surrounding the clinical relevance of reported visual improvements, and the natural history of the disease which may have a stable course without deterioration for long periods of time (Finger, 2010). Drusen may spontaneously regress and disappear without treatment. A well-designed study that confirms the results of earlier studies is required to assess the clinical benefit of rheopheresis in the treatment of AMD before this therapy can be recommended as a standard of care.

Technical notes

The majority of CS and trials used DFPP where plasma is first separated by membrane plasma separation and then passed through a plasma filter of appropriate pore size (rheofilter) where high-molecular weight substances are removed. Centrifugal plasma separation followed by plasma filtration has been alternatively used. Currently, the filtration devices necessary for this treatment are not licensed in the US but are available in Europe, Canada, and Asia.

Volume treated: 0.8-1.5 TPV	**Frequency:** 8 to 10 treatments (2/wk) over 8-21 wks
Replacement fluid: NA	

Duration and discontinuation/number of procedures

Clinical benefit of a single course of treatment has been reported to last for up to 4 years. Repeated treatment over several years has not been systematically investigated.

Keywords: age related macular degeneration, macular degeneration, rheopheresis, plasmapheresis, double filtration plasmapheresis

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AMYLOIDOSIS, SYSTEMIC

Incidence: Primary AL amyloidosis: 3-12/1,000,000/yr; DRA: Rare	**Indication**	**Procedure**	**Recommendation**	**Category**
	DRA	β_2-microglobulin column	Grade 2B	II
	Other causes	TPE	Grade 2C	IV
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
β_2-microglobulin column	1(36)	2(84)	1(345)	NA
TPE	0	0	0	8(9)

AL amyloidosis = monoclonal immunoglobulin light chain; DRA = dialysis-related amyloidosis

Description of the disease

Amyloidosis refers to a heterogeneous group of genetic and acquired disorders characterized by pathological extracellular deposition of insoluble polymeric fibrils consisting of misfolded proteins or protein precursors, leading to progressive organ damage. The familial disorders are rare and predominantly autosomal dominant, arising from missense mutations that lead to deposition of precursor proteins in tissues. The most common acquired disorders involve deposition of monoclonal immunoglobulin light chain (AL amyloidosis), serum amyloid A protein (AA amyloidosis) or β_2-microglobulin (dialysis-related amyloidosis [DRA]), but several other types of amyloidosis have been described such as transthyretin, fibrinogen A α-chain, leucocyte cell-derived chemotaxin 2, and apolipoprotein A1. AL amyloidosis is associated with multiple myeloma, Waldenström's macroglobulinemia, non-Hodgkin lymphoma, and primary plasma cell dyscrasia. Acquired factor X deficiency, acquired von Willebrand syndrome, coagulopathy due to liver failure and/or vascular fragility may contribute to a bleeding diathesis in approximately one quarter of patients with AL amyloidosis. AA amyloidosis is associated with chronic infection, malignancies or inflammation (e.g., Rheumatoid arthritis and hereditary periodic fever syndromes, including familial Mediterranean fever [FMF]) and predominantly affects the kidneys, leading to nephrotic syndrome and renal failure. DRA primarily affects bones, joints and soft tissues. Amyloidosis is a relatively rare disorder with estimated incidence of 3-12 per million patients per year for AL amyloidosis and 2 per million per year for AA amyloidosis. DRA is rare with current high flux dialysis membranes.

Current management/treatment

Approaches to therapy involve reducing protein precursor production, preventing aggregation, or inducing resorption. The goal of treatment for primary systemic AL amyloidosis is eradication of the underlying plasma cell disorder, thus the same chemotherapy regimens, targeted agents and autologous hematopoietic stem cell transplant approaches are used. End-organ complications are managed with symptomatic and supportive care. Management of coagulopathy includes infusion of plasma, cryoprecipitate, recombinant factor VIIa and/or bypass factors. Chemotherapy and splenectomy have also been anecdotally beneficial. AA amyloidosis is managed by aggressively treating the underlying inflammatory disorder. Colchicine is the main treatment for FMF to control the periodic fevers and tissue complications, including AA amyloidosis. Immunomodulatory and anti-cytokine regimens may also be beneficial for certain inflammatory disorders that lead to AA amyloidosis. In hereditary amyloidosis, organ transplantation is performed to replace amyloidotic organs or, in the setting of liver transplantation, reduce abnormal protein production. Initial findings were promising on the use of eprodisate as a targeted therapy to slow the progression of kidney disease in patient with AA amyloidosis; however, a phase III clinical trial failed to meet its primary endpoint. DRA can be managed with aggressive dialysis using membranes and treatment protocols that optimize clearance of β_2-microglobulin; however, kidney transplantation is the treatment of choice. Amyloid recurs in the transplanted kidney in 15% of cases reported in the literature. Bone and joint complications of DRA are managed symptomatically.

Rationale for therapeutic apheresis

CRs and small CS have described the use of TPE in patients with amyloid associated disorders. Due to concurrent immunosuppressive therapies, limited information on TPE procedures performed, and failure to establish improvement in symptoms is due to reduction in amyloid, the relative benefit of TPE is not clearly discernible. Intensive TPE with immunosuppressive treatment has been used to manage rapidly progressive glomerulonephritis with AA amyloidosis. In one report, regular TPE treatments over 8 months with melphalan and prednisone improved macroglossia and skin lesions and significantly reduced serum interleukin-6 levels in a patient with AL amyloidosis (Katayama, 1994). One CR described a transient, modest improvement in coagulation parameters with AL amyloidosis and factor X deficiency after TPE procedures with plasma replacement (Beardell, 1997). However, another report using a similar approach was ineffective in correcting AL amyloid associated severe factor X deficiency (Barker, 2004). No data exist supporting the use of TPE for neuropathy or other complications associated with AL amyloidosis, AA amyloidosis or DRA. Specialized adsorption columns or membrane filters to remove β_2-microglobulin have been used extensively in Japan for DRA. An RCT of 36 patients demonstrated a significant improvement in activities of daily living (ADL), stiffness, and pain scores in the β_2-microglobulin column group (n = 18) after 2 years (Gejyo, 2004). In a study of 17 patients, each acting as their own control, pinch strength and ADL scores were improved after one year of treatment (Abe, 2003). More recently, a survey of 138 institutions revealed that attending physicians considered β_2-microglobulin adsorption column treatment to be at least partially effective in greater than 70% of patients (n = 345) (Gejyo, 2013). LA has been demonstrated mechanistically to acutely lower some amyloid related proteins; however, further study is needed on clinical outcomes before this treatment can be recommended.

Technical notes

Volume treated: TPE: 1-1.5 TPV

Frequency: TPE: Varies; ß$_2$-microglobulin column - 3 times/week with dialysis

Replacement fluid: TPE: Albumin, plasma when coagulopathy present; ß$_2$-microglobulin column: NA

Duration and discontinuation/number of procedures

For DRA, clinical trials have reported outcomes after 1 or 2 years of treatment, but a survey of 345 patients reported a treatment period of 3.5 ± 2.7 years (range 9 months - 11 years). For TPE, the optimal duration and frequency is unknown; however, multiple procedures over the course of months have been used in some patients.

Keywords: amyloid, amyloidosis, systemic amyloidosis, light chain amyloidosis, ß$_2$-microglobulin, dialysis-related amyloidosis, familial Mediterranean fever

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ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE (GOODPASTURE SYNDROME)

Incidence: <2/1,000,000/yr	**Indication**	**Procedure**	**Recommendation**	**Category**
	DAH	TPE	Grade 1C	I
	Dialysis-independence	TPE	Grade 1B	I
	Dialysis-dependence*, no DAH	TPE	Grade 2B	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	1(17)	0	22(516)	NA

DAH = diffuse alveolar hemorrhage;
*At presentation, Cr ≥5.7 mg/dl indicates "dialysis-dependence"

Description of the disease

Anti-glomerular basement membrane (anti-GBM) disease is defined as the presence of small-vessel vasculitis which affects the glomerular capillaries, pulmonary capillaries, or both along with anti-GBM autoantibody deposition. The disease most commonly presents with rapidly progressive glomerulonephritis (RPGN); hematuria is a commonly presenting sign. Patients may experience a non-specific prodrome of fatigue, weight loss, and low-grade fevers. The typical finding on kidney biopsy is crescent formation within the glomeruli. Pulmonary hemorrhage is commonly present and may range from cough associated with a mild anemia reflective of blood loss within the alveoli to massive hemoptysis requiring invasive respiratory support. Anti-GBM antibodies are directed against the non-collagenous domain of the α3 chain of type IV collagen, causing activation of the complement cascade, resulting in tissue injury. At disease onset, approximately half will have severe or end stage renal failure; the proportion of crescents observed on biopsy correlates with the degree of renal failure at presentation. Anti-GBM disease is strongly associated with polymorphisms of MHC class II genes, with disease susceptibility correlating with HLA DRB1 alleles. Almost all patients have circulating anti-GBM antibodies in their blood at the time of diagnosis; a significant proportion will also have detectable ANCA. Patients exhibiting both antibodies typically present in a similar fashion to those with only anti-GBM antibodies but will have a different clinical course. Those with both antibodies experience early morbidity and mortality, present with more severe kidney and lung disease, and need prolonged immunosuppressive therapy due to higher frequency of relapse. Kidney biopsy in such patients reveals the typical crescents plus sclerotic glomeruli and tubulointerstitial fibrosis. Differential diagnosis includes granulomatosis with polyangiitis, systemic lupus erythematosus, microscopic polyangiitis, plus other systemic vasculitis and connective tissue diseases. The mainstay of therapy includes TPE for rapid clearance of antibodies plus immune suppressive medications (cyclophosphamide and corticosteroids) to prevent further antibody production; any potential inciting agents (hydrocarbon fumes, metallic dust, infection) should be eliminated. While RCTs have not been conducted, there is compelling evidence that morbidity and mortality have improved since the introduction of TPE. CRs of using rituximab either in addition to these therapies or in place of cyclophosphamide have been reported. It is important to identify the specific RPGN category in their patient as TPE protocols and responses differ. Prognosis of classical anti-GBM disease is strongly correlated to prompt initiation of therapy; relapse rarely occurs. Those most severely affected will ultimately need kidney transplantation; if no recovery of kidney function is seen in the first month of therapy, it is unlikely to improve.

Current management/treatment

Treatment includes the combination of TPE, cyclophosphamide, and corticosteroids. The role of rituximab needs to be established. Chronic immunosuppression is generally not required, except in patients with ANCA and anti-GBM antibodies. These patients respond rapidly to treatment, like anti-GBM, but can relapse, like those with ANCA-associated RPGN. Patients who progress to end stage renal disease (ESRD) may be treated with kidney transplantation after anti-GBM antibodies are undetectable. Although recurrence of linear IgG staining in the transplanted allograft is high (about 50%), these patients are usually asymptomatic and do not require TPE.

It is critical that TPE is implemented early in the course of anti-GBM nephritis. Several CS have demonstrated that most patients with creatinine <5.7 mg/dL recover renal function with treatment. Those with an initial creatinine ≥5.7 mg/dL or who are dialysis-dependent at the time of initiation of TPE usually will not recover kidney function due to irreversible glomerular injury. Such patients may not benefit from TPE and it should not be performed; DAH however should improve if present. DAH can be rapidly fatal or may have relatively mild manifestations; 90% of affected patients will respond. Therefore, a low threshold for initiating TPE is warranted in the presence of DAH. IA or DFPP with small pore plasma filters been used in small CS with efficient removal of anti-GBM antibodies (Biesenbach, 2014). Clinical benefit appears to be comparable to TPE, though randomized comparative studies have not been performed.

Rationale for therapeutic apheresis

Because of the knowledge that this disorder was associated with the presence of circulating, pathologic antibodies and the poor prognosis with treatments available at the time (90% would either die or require long-term hemodialysis), TPE was applied for treatment in the early 1970s. A single RCT involving a small number of patients demonstrated maintained kidney function and improved survival (Johnson, 1985). Additional benefits include a more rapid decline in anti-GBM antibody and resolution of hemoptysis. Reviews suggest that avoidance of ESRD or death will be achieved in 40-45% of patients.

Technical notes

In the setting of DAH, plasma should be used for part or whole of the replacement fluid.

Volume treated: 1-1.5 TPV	**Frequency:** Daily or every other day
Replacement fluid: Albumin; plasma when DAH present	

Duration and discontinuation/number of procedures

In most patients undergoing TPE and immunosuppression, anti-GBM antibodies fall to undetectable levels within 2 weeks; thus, the minimum course of TPE should be 10-20 days. The presence or absence of antibody should not be used to initiate or terminate therapy, because antibody is not demonstrable in a few patients with the disease and may be present in patients without active disease. In those patients with active disease, TPE should continue until resolution of evidence of ongoing glomerular or pulmonary injury.

Keywords: Goodpasture syndrome, diffuse alveolar hemorrhage, rapidly progressive glomerulonephritis, anti-GBM antibodies, ANCA, plasma exchange, immunoadsorption, double filtration plasmapheresis

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ATOPIC (NEURO-) DERMATITIS (ATOPIC ECZEMA), RECALCITRANT

Incidence: Children: atopic dermatitis 10-30%; adults: 1-3%; recalcitrant: rare		**Procedure**	**Recommendation**	**Category**
		ECP	Grade 2A	III
		IA	Grade 2C	III
		TPE/DFPP	Grade 2C	III
# reported patients: 100-300	**RCT**	**CT**	**CS**	**CR**
ECP	1(20)	2(45)	9(59)	NA
IA	0	6(100)	1(2)	NA
TPE/DFPP	0	1(9)	0	1(1)

Description of the disease

Atopic dermatitis (AD), or eczema, is the most common chronic relapsing skin disease seen in infancy and childhood. It affects 10-30% of children worldwide and frequently occurs in families with other atopic diseases. Infants with AD are predisposed to development for allergic rhinitis and/or asthma later in childhood, a process called "atopic march." AD is a complex genetic disorder that results in a defective skin barrier, reduced skin innate immune responses, and exaggerated T cell responses to environmental allergens and microbes that lead to chronic skin inflammation. Persistent skin inflammation may be associated with a relative lack of T regulatory cells in the skin. AD is characterized by T cell dysfunction, hypereosinophilia, and high levels of IgE. The latter is due to isotype switching to IgE synthesis by the cutaneous lymphocyte-associated antigen (CLA) + T-cells. IgE measurements or prick tests can identify allergens to which the patient is sensitized. AD often goes into remission as the patient grows older, leaving an adolescent or adult with skin prone to pruritus and inflammation when exposed to exogenous irritants; however, few individuals have life-long AD with severe symptoms.

Current management/treatment

The treatment of AD requires a systematic, multifaceted approach that incorporates skin hydration, topical anti-inflammatory therapy (including tacrolimus), identification and elimination of flare factors (especially foods), and, if necessary, systemic therapy. In refractory disease, phototherapy (UVA-1, UVB, or PUVA) are used. Treatments for third-line under investigation are interferon-γ, omalizumab, allergen immunotherapy, probiotics, Chinese herbal medications, and antimetabolites. Combination therapies are used to minimize side effects, especially from immunosuppressive drugs. In AD, the SCORAD (SCORing Atopic Dermatitis; a clinical tool for assessing the extent and severity of *AD*) is widely used for evaluating treatment success.

Rationale for therapeutic apheresis

Given the side effects of third-line therapies including immunosuppressive agents and phototherapies, ECP is used as a non-toxic and non-immunosuppressive alternative. Since 1994, CS and controlled studies in >100 patients have been published with a 70% of patients having a favorable response to ECP, requiring at least 6 cycles for a response. In one RCT, equivalence to cyclosporine therapy was shown (Kopplhus, 2014). ECP may be considered in a patient with AD who fulfils the following criteria: a diagnosis of severe AD of at least 12 months duration, SCORAD >45, resistance in the last 12 months to all first-line therapies used to treat AD, including topical steroids, topical calcineurin inhibitors, and one form of phototherapy or resistance to either systemic steroids or cyclosporine as second-line therapy.

IA decreases levels of IgE significantly. Both non-specific and IgE-specific columns have been used (Kasperkiewicz, 2018; Reich, 2018). Of note, only a short-term decrease of the serum IgE, followed by rapid recovery of IgE levels within 3 weeks after discontinuation of IA, was observed, whereas the skin-bound IgE in the dermis and epidermis (proved by biopsies) was reduced until the end of the observation period, 13 weeks after the initial IA. In parallel, decreased skin infiltration by inflammatory cells and improved skin architecture were observed.

TPE and DFPP are used to reduce IgE and immune complexes from patients' blood. For DFPP, there is one CT showing a significant improvement in symptoms.

Technical notes

Volume treated: ECP: Typically, MNCs are obtained from processing 1.5L of whole blood, but the volume processed may vary based on patient weight and HCT. The 2-process method collects and treats MNCs obtained from processing 2 TBV; IA: 2-4 TPV; TPE and DFPP: 1-2 TPV

Frequency: ECP: 1 cycle every 2 weeks for 12 weeks, then tapering; IA: series of up to 3-5 consecutive daily IA every 4 weeks up to 10-12 total; TPE and DFPP: weekly

Replacement fluid: TPE/DFPP: Albumin

Duration and discontinuation/number of procedures

The initial ECP treatment for AD is typically one cycle (2 treatments) every 2 weeks for 12 weeks, thereafter ECP treatment regimen depends on individual response, but is typically performed every 3-4 weeks, and then tapered to every 6-12 weeks before stopping. Relapse could be treated by returning to the interval frequency of the previously effective treatment schedule. In IA, 10-12 treatments are performed over for 4-6 weeks.

Keywords: recalcitrant, atopic dermatitis, immunoadsorption, plasma exchange, extracorporeal photopheresis

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AUTOIMMUNE HEMOLYTIC ANEMIA, SEVERE

Incidence: <1/100,000/yr	**Indication**	**Procedure**	**Recommendation**	**Category**
	Severe CAD	TPE	Grade 2C	II
	Severe WAIHA	TPE	Grade 2C	III
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
CAD	0	0	2(6)	29(30)
WAIHA	0	0	3(14)	34(37)

CAD = cold agglutinin disease; WAIHA = warm autoimmune hemolytic anemia

Description of the disease

Autoimmune hemolytic anemia (AIHA) represents a group of disorders in which autoantibodies mediate either intravascular hemolysis by the terminal lytic complex (C5b-C9) or, more often, extravascular destruction in the spleen by the macrophage-phagocytic system. The presenting symptoms include fatigue and jaundice. The laboratory findings are hemolysis (anemia, hyperbilirubinemia, elevated serum LDH) with a positive direct antiglobulin (Coomb's) test (DAT). AIHA can be classified into two major types, warm autoimmune hemolytic anemia (WAIHA) and cold agglutinin disease (CAD)/cold autoimmune hemolytic anemia (CAIHA). Warm autoantibodies consist of IgG hemolysins that react optimally at 37°C and some may demonstrate relative specificity to RBC antigens. Causes of WAIHA include idiopathic (30% of cases), secondary (associated with underlying autoimmune diseases, lymphoproliferative disorders, infections, or after HSCT/solid organ transplantation) and drug-induced (e.g., methyl-dopa, cephalosporins, and tacrolimus). In WAIHA, the DAT is positive with anti-IgG and potentially anti-C3b. CAD results from IgM autoantibodies that react optimally at 0-5°C and may be directed against the I/i antigens. It is typically seen in the post-infectious setting (as polyclonal autoantibodies) or in lymphoproliferative disorders (as monoclonal autoantibodies). The cold-reactive IgM autoantibody produced after *Mycoplasma pneumoniae* infection typically has anti-I specificity, whereas the autoantibody associated with Epstein-Barr virus infection (infectious mononucleosis) demonstrates anti-i specificity. In CAD, the DAT is positive with anti-C3b only. The severity of hemolysis in AIHA may be influenced by the autoantibody titer, avidity to RBC antigens, ability to fix complement, and, for cold autoantibodies, most importantly thermal amplitude. The thermal amplitude is defined as the highest temperature at which the antibody reacts with its cognate antigen. A cold autoantibody with high thermal amplitude can be active within a range of temperatures attainable in vivo.

Current management/treatment

Therapy for WAIHA is typically initiated with prednisone (1-2 mg/kg/day) and continued until an adequate response is attained. Prednisone suppresses antibody production and down-regulates Fc-receptor-mediated hemolysis in the spleen. Splenectomy, despite being underutilized, is perhaps the most effective and best-evaluated second-line therapy, but there is limited data on long-term efficacy. Rituximab is another second-line therapy with documented short-term efficacy, and limited information on long-term efficacy. The RAIHA RCT showed efficacy of prednisone plus rituximab as first-line therapy in WAIHA (Michel, 2016). Other modalities used in refractory cases include IVIG, cyclophosphamide, vincristine, mycophenolate mofetil, azathioprine, sirolimus, and monoclonal antibodies such as alemtuzumab. One CR showed efficacy with eculizumab (Ma, 2016). In patients with CAD and severe hemolytic anemia, treatment primarily involves avoiding exposure to cold. In patients with severe disease, the most effective and best-evaluated treatment is rituximab, which is recommended as first-line therapy, although complete and sustained remissions are uncommon. The Nordic prospective nonrandomized multicenter trial showed efficacy of bendamustine plus rituximab in 32 of 45 patients with CAD (Berensten, 2017). Prednisone is usually ineffective, as is splenectomy, because the liver is the dominant site of destruction of C3b-sensitized RBCs. with secondary CAD typically respond well to anti-lymphoma chemotherapy.

Rationale for therapeutic apheresis

TPE may remove pathogenic immune complexes, activated complement components, and circulating autoantibodies. TPE is typically utilized in patients with fulminant hemolysis who are unresponsive to RBC transfusion and/or steroid therapy. TPE treatment may temper the disease course until a more aggressive immunosuppressive therapy takes effect, or if other treatments have failed. In WAIHA, several CRs and CS have shown favorable results with the use of TPE. However, others demonstrate no effect. In one CS utilizing TPE in the setting of severe WAIHA, TPE versus no TPE did not demonstrate differences in increase in hemoglobin levels post-transfusion (Ruivard, 2006). One retrospective study reported on the use of whole blood exchange (WBE) for severe AIHA (Li, 2015). IgM autoantibodies in CAD are primarily intravascular and thus might effectively be removed by TPE. In addition, TPE might be beneficial in patients with CAD before surgeries requiring hypothermia (Barbara, 2013). One CR described the management of CAD in off-pump coronary artery bypass surgery with an intravascular warming catheter instead of TPE (Tholpady, 2016). Improvement of AIHA after TPE is usually temporary, depending on the characteristics and rate of production of the autoantibody and thus, should be combined with concomitant immunosuppressive therapy. Case reports have claimed success using TPE as a "primer" for IVIG, cyclophosphamide treatment, or bortezomib (e.g., synchronization of 1-3 daily sessions of TPE followed by pulse treatments with cyclophosphamide and prednisone).

Technical notes

If the thermal amplitude of an IgM cold autoantibody is such that agglutination occurs at room temperature, RBC agglutination may occur within the cell separator and tubing. In these situations, therapy may require a controlled, high temperature setting of 37°C both in the room and within the extracorporeal circuit.

Volume treated: 1-1.5 TPV	**Frequency:** Daily or every other day
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

Until hemolysis decreases and the need for transfusions is limited or until immunosuppressive therapy takes effect.

Keywords: Autoimmune hemolytic anemia, cold agglutinin disease, direct antiglobulin test, plasma exchange, warm autoimmune hemolytic anemia

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BABESIOSIS

Incidence: 4,600 cases in the US since 1986; endemic in Northeast and Great Lakes regions	**Indication**	**Procedure**	**Recommendation**	**Category**
	Severe	RBC exchange	Grade 2C	II
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	4(20)	19(20)

Description of the disease

Babesiosis is a tick-borne zoonosis caused by an intraerythrocytic protozoan. The species that most commonly infect humans are: *B. microti* (the predominant US pathogen), *B. duncani*, *B. divergens*, *B. venatorum*, and M01-type *Babesia sp.* Ninety-five percent of cases in the US are in the Northeast and Upper Midwest, but cases have been reported in almost every state. Although the seroprevalence in Connecticut is 0.3-17.8%, the number of reported cases is only 44 per 100,000. The disease is usually transmitted from an animal reservoir to humans by the bites of *Ixodes* ticks, usually between May through October. Babesiosis can be also transmitted by blood products, mostly RBCs from asymptomatic blood donors, and transmitted vertically. The incubation period is usually 1-3 weeks, with longer incubation periods (usually 6-9 weeks) reported with transfusion transmission. Three types of distinct presentations have been described: (1) Asymptomatic infection, which can persist for months-years; (2) Mild-moderate illness, the most common presentation, characterized by the gradual onset of malaise and fatigue followed by intermittent fever and one or more of the following: chills, sweat, anorexia, headaches, myalgia, arthralgia, and cough. Patients often have thrombocytopenia and anemia. The illness usually lasts weeks-months, occasionally with prolonged recovery lasting greater than a year with or without treatment; (3) Severe disease generally occurs in people with underlying immunosuppressive conditions, including HIV, malignancy, immunosuppressive medication, and after splenectomy. Other risk factors include age >50 and simultaneous co-infection with Lyme disease. Symptoms in severe disease include acute respiratory failure, disseminated intravascular coagulopathy (DIC), congestive heart failure, acute liver and renal failure, and hemolytic anemia. Excessive cytokine production is thought to be a major cause of severe babesiosis and is associated with tissue pathology that can lead to significant end-organ damage and can result in persistent relapsing disease or death. The all-cause mortality is <1% of clinical cases and about 10% in transfusion transmitted cases, though mortality can be up to 20% in immunocompromised patients with severe babesiosis. Diagnosis is through microscopic identification of the organism using Giemsa-stained thin blood smear, PCR, and/or serologic testing. The detection of IgM is indicative of recent infection while IgG titer of ≥1,024 usually signifies active and/or recent infection. About 1-10% of the RBCs are parasitized in immunocompetent hosts, but seldom exceeds 5%. In immunocompromised hosts, parasitemia up to 85% has been described.

Current management/treatment

Primary therapy for mild-moderate disease includes antibiotics. Most people can be successfully treated with atovaquone and azithromycin administered for 7-10 days. Combination of quinine sulfate and clindamycin is equally effective but associated with more adverse reactions and usually reserved for patients with severe disease. RBC exchange is indicated for babesiosis patients with heavy parasitemia (typically >10%) or who have significant comorbidities such as significant hemolysis, DIC, pulmonary, renal, or hepatic compromise. In persistent relapsing disease, antibiotics should be given for a minimum of 6 weeks and for at least 2 weeks after the last positive blood smear with ongoing monitoring.

Rationale for therapeutic apheresis

RBC exchange might influence the course of the disease by 3 possible mechanisms of action: (1) lower the level of parasitemia by replacing infected RBCs with non-infected donor RBCs; (2) removal of rigid infected cells to decrease microcirculation obstruction and tissue hypoxia caused by adherence of RBCs to vascular endothelium; and (3) removal of cytokines produced by the hemolytic process, including INF-α , TNF-α, IL-1, IL-6, nitric oxide, and thromboplastin substances, which can promote renal failure and DIC. The greatest advantage of RBC exchange over antibiotic therapy is its rapid therapeutic effectiveness though questions remain as to the effect on morbidity/mortality and exact mechanism of benefit. In severe cases, the benefits may outweigh the risks of the procedure, mainly exposure to multiple RBC transfusions.

Technical notes

Automated apheresis instruments calculate the volume of RBCs required to achieve the desired post-procedure HCT, fraction of RBCs remaining and, by inference, the estimated final parasite load. A 2-volume RBC exchange can reduce the patient RBCs to roughly 10-15% of the original. In critically ill patients who failed antimicrobials and/or RBC exchange, the use of TPE has been also reported. For patients with severe coagulopathy, plasma may be incorporated into replacement fluid, either by performing whole blood exchange or TPE.

Volume treated: 1-2 total RBC volume(s)	**Frequency:** Single procedure but can be repeated
Replacement fluid: Leukoreduced RBCs (or other as above)	

Duration and discontinuation/number of procedures

The specific level of parasitemia to perform RBC exchange is unclear but >10% parasitemia in the presence of severe symptoms is the most commonly used guideline to initiate the procedure. The specific level to which parasitemia must be reduced to elicit the maximum therapeutic effect is also unclear. Treatment is usually discontinued after achieving <5% residual parasitemia. Decision to repeat the exchange is based on the level of parasitemia post-exchange as well as the clinical condition (ongoing signs and symptoms). Treating physicians should be aware, however, of the potential for rebound in parasitic burden post-RBC exchange and thus, post-exchange parasitemia surveillance is crucial (Alquist, 2017).

Keywords: Babesia, parasitemia, red blood cell exchange, erythrocytapheresis

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BURN SHOCK RESUSCITATION

Incidence: 50,000 admissions for burn injuries/yr		Procedure	Recommendation	Category
		TPE	Grade 2B	III
# reported patients: 100-300	**RCT**	**CT**	**CS**	**CR**
	1(17)	2(66)	6(102)	NA

Description of the disease

Major thermal injury involving >25% total body surface area (TBSA) results in clinically significant, potentially fatal physiologic consequences. Increased capillary permeability and intravascular volume deficits predispose to cellular shock releasing inflammatory mediators due to diminished organ perfusion. Disruption of the sodium-potassium membrane pump results in an intracellular sodium shift contributing to progressive hypovolemia. Heat injury causes release of inflammatory mediators with subsequent vasodilation and capillary leakage. Decreased myocardial contractility and inappropriate cardiac output may produce hemodynamic fragility. Acute respiratory distress (ARDS) may occur from inhalational injury or excessive edema. Life threatening infections occur due to suppressed leukocyte chemotactic function, lymphocyte suppression, and loss of skin barrier.

Current management/treatment

The treatment in the immediate post-burn period is aggressive intravenous fluid resuscitation with crystalloid, though colloid solutions may be included, typically starting 12 to 24 hours post burn as part of salvage therapy. American and European guidelines indicate that the volume of fluid resuscitation is typically 2-4 mL/kg body weight/% TBSA of crystalloid in the first 24 hours. Goals are to maintain urine output (UOP) while balancing risks of edema, ARDS, and organ hypoperfusion. Fluid resuscitation is successful in most burn patients. Patients with full-thickness burns, inhalation injury or resuscitation delay may have greater fluid requirements.

Rationale for therapeutic apheresis

The theoretical benefit of TPE in the setting of acute burn shock is based on removing circulating factors such as inflammatory mediators or other humoral substances participating in major burn pathophysiology. Replacement with plasma may decrease capillary permeability and improve intravascular oncotic pressure, which might improve response to fluid resuscitation, mean arterial pressure (MAP), UOP, and immune function. In the only reported RCT of TPE in burn resuscitation, TPE did not alter the course of burn shock in 17 patients (9 TPE, 8 control arm) (Kravitz, 1989). However, the TPE group had significantly higher mean full-thickness burn injury and earlier completion of resuscitation. There were 3 deaths in the TPE group versus none in the control group. A retrospective historic CT of 40 patients found TPE increased MAP and UOP in the treated group and decreased the estimated intravascular fluid volumes required for resuscitation by 30% (Neff, 1989). Mortality was higher than predicted in both groups but was not statistically different between the two groups. However, the TPE treated group had more severe burns, thus higher mortality would have been predicted. Finally, a trial looking at immunologic parameters in 26 burn patients compared 13 patients who underwent TPE to those who had not with regard to a variety of immunologic markers (Stratta, 1986). No differences were seen except that serum from patients undergoing TPE had less suppression of the mixed lymphocyte reaction ($p<0.10$). The TPE group had greater extent of burn injury and longer hospitalization but similar mortality to those patients who had not received TPE. Of the limited published CS, a variety of favorable physiologic effects were reported with respect to fluid resuscitation, UOP, cardiac function and immune benefits. Clinical outcome data were not consistently available. In one CS, TPE was applied in 5 clinical settings: failed fluid resuscitation, myoglobinuria, respiratory failure ARDS, metabolic "exhaustion", and documented sepsis; however, the endpoint for clinical follow-up was not defined in this study (Ninnemann, 1984). Overall mortality with TPE was 32% without a control group for comparison, with 2 early deaths attributed to irreversible burn shock and 4 late deaths due to sepsis. A CS of 37 patients found statistically significant increased UOP and decreased crystalloid volume needed when comparing these parameters 3 hours before and 3 hours after TPE (Klein, 2009). Further investigation with well-designed RCTs is needed to establish the efficacy and safety of TPE. The American Burn Association acknowledges that TPE is sometimes applied empirically as a salvage therapy; it has identified the use of TPE in burn resuscitation as an area for research because of the lack of level 1 evidence (Gibran, 2013).

Technical notes

TPE is instituted early in the post-burn period, typically 8-16 hours after injury. Patients treated with TPE typically have >20-50% TBSA burns and are refractory to fluid resuscitation in most reports. TPE has also been used at later time points in the management of thermal injury, for indications other that resuscitation. In a retrospective historic CT, TPE was initiated if the total resuscitation volumes exceeded 1.2X the volume predicted by the modified Baxter formula (3 mL Lactated Ringer's solution/kg actual body weight/%TBSA burn). Failure of conventional IV fluid resuscitation is defined as UOP 30 mL/hr and/or MAP <65 mmHg in the setting of increasing IVF volumes. The choice of replacement fluid is dependent on the indication for TPE, concomitant infection, and bleeding risk.

Volume treated: 1.5 TPV	Frequency: Once, see below
Replacement fluid: Albumin, plasma	

Duration and discontinuation/number of procedures

TPE is typically performed within the first 24 hours (8-16 hours) with additional 1-2 TPE procedures in selected patients whose MAP and UOP do not increase or whose IV fluid volumes do not decline to predicted volumes (second TPE within 6-8 hours of first). In several CS, patients were also included that received TPE at later time points, often for indications other than resuscitation.

Keywords: burn, shock, resuscitation, thermal injury, heat injury, plasma exchange

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CARDIAC NEONATAL LUPUS

Incidence: 2% anti-SSA positive mothers		**Procedure**	**Recommendation**	**Category**
		TPE	Grade 2C	III
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	4(20)	13(15)

Description of the disease

Congenital lupus can result in dermatologic, hematologic, hepatic, musculoskeletal, and CNS manifestations. Congenital lupus affecting the cardiovascular system can result in congenital heart block (CHB) and cardiomyopathy. CHB is an acquired immune mediated disease caused by passive transplacental transfer of maternal antibodies beginning at 12-weeks gestational age (GA). Most commonly anti-Ro (anti-SSA [Sjögren syndrome-A]) alone, or in combination with anti-La (anti-SSB [Sjögren syndrome-B]), or anti-ribonuclear protein antigens [RNP] antibodies are the cause. CHB can result from the binding of the antibodies to fetal cardiac cells (undergoing physiologic apoptosis secondary to remodeling) resulting in autoimmune injury and fibrosis of the atrioventricular node and associated tissues. This predominately occurs between 18-24 weeks GA but can happen throughout the pregnancy. The antibodies may also block calcium channels within the myocardium resulting in inflammation and fibrosis, leading to endocardial fibroelastosis (EFE) and progression to heart failure, hydrops fetalis, and death. Two percent of mothers positive for anti-SSA and 1% of mothers with SLE have children with CHB. Recurrence rate in a mother with antibodies and a previously affected child is approximately 18%. Mothers may be asymptomatic (22-40% asymptomatic; 50% develop autoimmune symptoms later) or have systemic lupus erythematosus (SLE), Sjögren syndrome, antiphospholipid syndrome, or other autoimmune tissue disorders. Forty-one percent of neonates have at least one other affected sibling. Genetics and environment appear to play a role in disease manifestation; fraternal twins may not both demonstrate CHB and incidence is higher in winter. With 2nd or 3rd degree AV block, 91% survive birth with 93% of the survivors living through the neonatal period, and 2/3 requiring a pacemaker by 1 year. Death is associated with earlier onset of disease (GA <20 weeks), ventricular rate ≤50 bpm, fetal hydrops, and impaired left ventricular function. Fetal/neonatal mortality is higher in non-whites and older maternal age. Prenatal diagnosis is made by fetal echocardiogram, which demonstrates varying degrees of CHB and diffuse thickening of endocardium with or without ventricular dysfunction or hydrops. Postnatally, neonates can present with clinical manifestation of the skin, persistent neonatal bradycardia with electrocardiogram consistent with CHB, or with only electrocardiogram changes.

Current management

The current recommendation is for pregnant women with positive SSA ± SSB antibodies to have fetal cardiac evaluation every 2-3 weeks from 18-28 weeks GA to evaluate cardiac rhythm and function. Treatment is either prophylactic, when a mother has had a previously affected fetus/neonate, or symptomatic when CHB is detected in the current pregnancy. The mainstay of maternal treatment is fluorinated glucocorticoids and β-agonists; adjuvant therapies include TPE, IVIG, hydroxychloroquine, and other immunosuppressive agents. One study postulated that initiation of maternal hydrochloroquine (HCQ) therapy prior to 10-week GA in women with anti-SSA/SSB and a previously affected child may decrease CHB in the current pregnancy. A trial is currently enrolling, Preventive Approach to Congenital Heart Block with Hydroxychloroquine (PATCH), to look at the effect of HCQ on pregnant mothers with antibodies to Ro/La to prevent CHB in offspring. IVIG has been found to lower titers of the causative antibody by 80%, although mothers with high Id: anti-Id ratio had no effect. The Preventive IVIG Therapy for Congenital Heart Block (PITCH) study enrolled 20 mothers, who were given low-dose IVIG (400 mg/kg every 3 week) starting at 12-24-week GA, which did not prevent recurrence (Friedman, 2010). Treatment of the mother for fetal reversal of 3rd degree CHB has not been achieved, but it has been stabilized. 1st or 2nd degree CHB can be reverted to normal sinus rhythm in some studies.

Rationale for therapeutic apheresis

Since CHB is caused by antibodies, removal of maternal antibodies by TPE may potentially prevent or reverse fetal/neonatal disease. Multiple CS and CRs have been published with varying success and regimens. TPE regimens varied from 3 procedures per week, weekly, every other week, to monthly. All patients received steroids and often received IVIG or azathriopine. In 3 patients with anti-SSA and mild fetal cardiac involvement who received IVIG, TPE, and steroids, fetal cardiac disease was halted, and none required a pacemaker (Martinez-Sanchez, 2015). Another CS of 6 patients (3 with 2nd CHB and 3 with 3rd CHB), described a regimen of TPE given 2 consecutive days then weekly until delivery, consisting of 70-100% volume exchange with 4% albumin; betamethasone (4 mg/day) then prednisone taper postpartum; and IVIG pre- and post-delivery (1 g/kg/day) at 15-day intervals; and low dose aspirin (Ruffatti, 2013). The fetuses with 2nd degree CHB reverted to normal conduction during pregnancy while those with 3rd degree CHB remained stable or improved. This group used a similar regimen for 2 previous (successful reversion of 2nd degree) and 4 future (no eversion of 2nd or 3rd degree) pregnancies. In pregnancies that responded, antibody titers fell long-term. A single CS of 4 patients using IA has been reported, which demonstrated prevention but not treatment of disease (Claus, 2006).

Technical notes

One case had small placental hemorrhage, which could have been due to anticoagulation during and after TPE. Apheresis of pregnant patients should always be performed with caution and multidisciplinary support.

Volume treated: 1 TPV	**Frequency:** 3/wk to weekly to monthly
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

TPE regimens varied substantially. Some only treated until antibody levels decreased and stayed low.

Keywords: cardiac neonatal lupus, congenital heart block, anti-Ro (anti-SSA), anti-La (anti-SSB), anti- ribonuclear protein antigens, cardiomyopathy, plasma exchange, autoimmune, neonatal lupus erythematosus, Sjogren's syndrome

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CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME (CAPS)

Incidence: Rare; 502 patients in CAPS Registry as of December 2015		**Procedure**	**Recommendation**	**Category**
		TPE	Grade 2C	I
# reported patients: 100-300	**RCT**	**CT**	**CS**	**CR**
	0	0	5(192)*	NA

*Includes CAPS registry data (which includes cases reported directly to the CAPS registry or published CRs and CS up through December 2015 (Rodríguez-Pintó, 2018) and additional subsequent published CS.

Description of the disease

The antiphospholipid syndrome (APS) is an acquired hypercoagulable state characterized by one or more episodes of venous and/or arterial thrombosis and/or obstetric complications in a patient with laboratory evidence of persistent antiphospholipid antibodies such as lupus anticoagulant (LA), anticardiolipin (aCL) and/or anti-β2-glycoprotein I (anti-β2GPI). Catastrophic APS (CAPS) is defined as the acute onset of multiple thromboses in at least 3 organ systems over a period of days or weeks, in patients with antiphospholipid antibodies. The most commonly affected sites by thrombosis are small vessels of the kidneys, lungs, brain, heart and skin, although large vessel thrombosis may also occur. Common manifestations of CAPS include renal insufficiency, acute respiratory distress syndrome, pulmonary embolism, encephalopathy, stroke, heart failure, myocardial infarction, livedo reticularis, and skin necrosis. In addition, the systemic inflammatory response syndrome (SIRS) is a component of the acute phase of CAPS. CAPS may be the first manifestation of APS ("de novo") or a complication in the clinical course of patients known to have the syndrome. It is unknown why a minority of patients with APS present with a catastrophic picture, although HLA class II genes and genetic thrombophilia may be predisposing factors. An environmental trigger also seems to be necessary. In the CAPS Registry through 2015, 65% of episodes were associated with precipitating factors, which preceded the clinical diagnosis of CAPS: infection was the most common finding, identified in 49% of the episodes, followed by surgery (17%), malignancy (16%), contraceptives (10%), pregnancy related (8%), and other (23%) (Rodríguez-Pintó, 2016). The presence of antiphospholipid antibodies among episodes of CAPS was LA 83%, aCL IgG 81%, aCL IgM 49%, anti-β2GPI IgG 78%, and anti-β2GPI IgM 40%. Other laboratory features of CAPS include thrombocytopenia (67%) and schistocytes on the peripheral blood smear (22%). The differential diagnosis includes sepsis, disseminated intravascular coagulopathy, heparin-induced thrombocytopenia, HELLP syndrome, thrombotic thrombocytopenic purpura, and hemolytic uremic syndrome.

Current management/treatment

The optimal treatment of CAPS is unknown since there have been no prospective studies due to the low incidence of the condition. However, the therapeutic approach has 3 clear aims: treat any precipitating factors, prevent and control ongoing thrombosis, and suppress the excessive cytokine production. A triple therapy approach of anticoagulation plus glucocorticosteroids plus TPE and/or IVIG is the recommended approach to therapy (Legault, 2018); however, combinations of these approaches and additional treatment strategies have also been utilized. Based on the CAPS Registry cohort, this triple therapy approach was independently associated with higher survival among CAPS patients. The mortality rates in patients treated with triple therapy, drugs included in the triple therapy but in other combinations, or none of the treatments included in the triple therapy were 29%, 41%, and 75% respectively (Rodríguez-Pintó, 2018). Mortality in patients who received triple therapy with both IVIG and TPE was similar to those that received triple therapy with either IVIG or TPE, thus it may not be necessary to administer both to patients. Several other therapeutic options have been tried in patients, particularly in refractory or relapsing cases, including cyclophosphamide, rituximab, and eculizumab.

Rationale for therapeutic apheresis

The exact mechanism for TPE benefit in CAPS is not known, although the removal of antiphospholipid antibodies, cytokines, tumor necrosis factor-α, and complement likely plays an important role.

Technical notes

Plasma as the replacement fluid repletes natural anticoagulants such as antithrombin and proteins C and S. Two successful reports using albumin as replacement fluid may suggest plasma may not be always necessary in CAPS (Marson, 2008). Since plasma provides antithrombin, which is essential to mediate anticoagulation with heparin, the use of albumin alone as replacement fluid may prevent the beneficial effect of heparin anticoagulation, unless levels of antithrombin and heparin anticoagulation are adequate by laboratory monitoring. Thus, it is possible that a combination of plasma and albumin would provide the necessary benefit of TPE and minimize potentially serious and undesirable side-effects from excessive exposure to plasma.

Volume treated: 1-1.5 TPV	**Frequency:** Daily or every other day
Replacement fluid: Plasma alone or in combination with albumin	

Duration and discontinuation/number of procedures

Most published cases have reported daily or every other day TPE for a minimum of 3-5 days up to courses of 1-3 weeks, but some patients have been treated with longer courses. Clinical response dictates the duration of TPE; no single clinical or laboratory parameter is used to determine when to discontinue treatment. Some have followed antiphospholipid antibody titers to monitor response to treatment (Flamholz, 1999).

Keywords: catastrophic antiphospholipid syndrome, antiphospholipid syndrome, lupus anticoagulant, anticardiolipin antibodies, anti-β_2-glycoprotein I, plasma exchange

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CHRONIC FOCAL ENCEPHALITIS (RASMUSSEN ENCEPHALITIS)

Incidence: Rare; ~2/1,000,000 under age 18 years		**Procedure**	**Recommendation**	**Category**
		TPE	Grade 2C	III
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	2(9)	8(11)

Description of the disease

The syndrome of Rasmussen encephalitis (RE) was first described in 1958. RE is a rare, inflammatory, and possibly immune mediated disease characterized by unilateral inflammation of the cerebral cortex. The two cardinal symptoms are progressive neurological deficits and intractable seizures, often in the form of epilepsia partialis continua and recurring epileptic status. Distinctive magnetic resonance imaging (MRI) features include progressive unilateral focal cortical atrophy and gray or white matter high-signal changes with basal ganglion involvement. Onset is typically in childhood (mean age 6 years) but a similar syndrome has been described in adults. Late onset presentations are characterized by a slower clinical course and less serve neurologic deficits. Several patients have presented with progressive neurologic decline without seizures. The etiology is unknown, but antecedent infection with Epstein-Barr virus, herpes simplex virus, enterovirus, or cytomegalovirus has been implicated. Cytomegalovirus genome has been found in resected cortical tissue of 3 adult patients with RE. Cerebrospinal fluid analysis is typically normal, although mild lymphocytic pleocytosis and elevated protein may be found. Histopathologic features show microglial and lymphocytic nodules with perivascular cuffing, neuronal death, and neurophagia progressing to cortical cavitation, astrogliosis, and neural loss. These findings suggest both immune mediation of both adaptive immunity via T lymphocyte responses, and innate immunity characterized by microglia and astroglia. MRI of the brain is the mainstay for diagnostic assessment and follow-up as no specific EEG abnormalities can distinguish RE from other types of focal epilepsy.

Current management/treatment

Treatment aims to reduce seizure activity and frequency and improve functional long-term outcome, as measured by both motor and cognitive performance. Anticonvulsants are necessary but not always effective, nor do they arrest progression. Subtotal, functionally complete hemispherectomy may markedly reduce seizure activity in most patients but at the price of irreversible neurological deficits. In general, immunotherapy slows disease progression, but none has halted nor cured the disease, and has a lesser effect on total seizure burden. Intravenous methylprednisolone and oral prednisone given for up to 24 months in a tapering schedule may help to diminish the intractable focal seizures and motor deficits during the first year of onset and before hemiplegia develops. IVIG (dosed up to 2 g/kg over 2-5 days, then repeated monthly if there is a response) may be tried prior to a trial of steroids in patients with established disease and may modestly improve the hemiparesis. Some authors recommend intravenous methylprednisolone (400 mg/m^2 every other day for 3 infusions followed by monthly infusions for the first year) and prednisone (2 mg/kg/day tapered over 1-2 years) if further treatment is needed. Intraventricular interferon-α given via Omaya reservoir, intravenous rituximab, and tacrolimus have been investigated for control of epileptic and neurological aspects of RE. In a CR, use of natalizumab was reported to decrease seizure frequency (Bittner, 2013). Ganciclovir has been also used and showed some therapeutic effect in patients treated early after symptom appearance (1-3 months). Given that the severity of symptoms varies among different patients and phases, the therapeutic strategy, including medical and surgical options, must be tailored to the need of each patient.

Rationale for therapeutic apheresis

Patients may have autoantibodies, against several neural molecules, that may be produced in the CNS after cytotoxic T cell-mediated neuronal damage. However, there is no consistent association with specific autoantibodies in plasma or cerebrospinal fluid. The demonstration of serum immunoreactivity to the glutamate receptor GluR3 in 3 individuals with histologically confirmed RE led to the use of TPE in a 9-year-old girl (Rogers, 1994). Seven single-volume TPE procedures performed over 3 weeks followed by weekly TPE for 4 weeks resulted in marked reduction in GluR3 immunoreactivity and significant clinical improvement (decreased frequency of seizures, resumption of playing with dolls, and riding a bicycle) during the first 7 weeks of treatment. Serum GluR3 immunoreactivity spontaneously rose over the subsequent 4 weeks and she deteriorated clinically but had transient responses to a repeat course of therapy. Other reports indicate that serum GluR3 immunoreactivity, which was found in only few patients with RE, is a feature of epilepsy syndromes and not specific to RE. However, other brain autoantibodies have also been identified in RE patients. Clinical and EEG parameters of epileptogenesis were transiently diminished by TPE in two other patients. Monthly courses of IA using staphylococcal protein A diminished seizure frequency and halted cognitive deterioration in a 16-year-old girl with IgG anti-GluR3 antibodies over a 2-year period, and controlled status epilepticus in a 20-year-old woman (Antozzi, 1998). Despite the paucity of reports, a concerted trial of immunotherapy, including apheresis, to control seizures, mitigate functional decline, and delay the need for hemispherectomy in patients with RE could be considered.

Technical notes

Neuropsychological assessment may be helpful in evaluating patients with slowly progressive disease to determine whether TPE is effective in postponing surgical therapy. Use of TPE, or IA is limited to few cases.

Volume treated: 1-1.5 TPV with TPE; IA: up to 2.5 TPV	**Frequency:** An initial course of 5-6 TPE, or IA treatments in most cases will result in transient improvement, and must be adjusted to the individual response and concomitant immunosuppressive treatment.
Replacement fluid: TPE: Albumin; IA: NA	

Duration and discontinuation/number of procedures

After an initial course of treatment subsequent courses of TPE (with or without IVIG), or IA may be performed at intervals of 1 to several weeks for a period up to 9 months as empirically needed to maintain clinical stability and avoid or delay hemispherectomy. Immunosuppressive medications may increase the interval between courses.

Keywords: Rasmussen encephalitis, chronic focal encephalitis, TPE, IA

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CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (CIDP)

Prevalence: 2-3/100,000		**Procedure**	**Recommendation**	**Category**
		TPE/IA	Grade 1B	I
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
TPE	3(67)	0	37(1056)	NA
IA	2(33)	0	1(14)	4(4)

Description of the disease

Chronic inflammatory neuropathies are a heterogeneous group of disorders caused by autoimmune inflammation of peripheral nerves. They mainly include chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), and neuropathy associated with an IgM monoclonal gammopathy (see Paraproteinemic demyelinating neuropathies fact sheet). Most patients with these neuropathies respond to immune therapies even if their effect varies in the different forms. CIDP typically develops over 2 months and may have a chronic progressive or a relapsing course affecting the sensory and motor nerves while an autonomic impairment is uncommon. Atypical variants of CIDP have been described including Lewis-Sumner syndrome (multifocal acquired demyelinating sensory and motor neuropathy, MADSAM), distal acquired demyelinating (DADS) neuropathy, purely motor, purely sensory, and focal CIDP. CIDP is a severe disease with over 50% of the patients having a severe disability in the course of the disease leading to inability to walk without support and approximately 10% eventually become persistently disabled or die because of the illness. Cerebrospinal fluid (CSF) protein is elevated and evidence of demyelination is present on electrophysiological testing. CIDP can occur in conjunction with other disorders such as HIV and diabetes. It can be difficult to distinguish acute-onset CIDP from Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy; AIDP) (see separate sheet). Similar clinical presentations may be seen with inherited, paraneoplastic and toxic neuropathies, and neuropathies associated with nutritional deficiency, porphyria, or critical illness.

Current management/treatment

There are 3 first-line treatment options: intravenous or oral corticosteroids, which are commonly used, IVIG, or TPE. Evidence from CTs is in favor of IVIG or TPE. The initial choice is often based on ease of administration, cost, availability, and side effects. Therapies should be initiated early to stop the inflammatory demyelination and prevent secondary axonal degeneration and permanent disability. Individuals may differ in response to any one of these modalities possibly due to the heterogeneity of CIDP. Therapeutic response is measured by improvement or stabilization of individual neurological symptoms, providing guidance at which point treatment can be tapered or discontinued. Sixty to 80% respond to initial therapy but long-term prognosis varies. Correct diagnoses must be considered for patients who are refractory to more than one of first-line treatments. Maintenance therapy, including steroids, periodic TPE, or repeated infusion of IVIG, is required in 40-65% of patients due to relapse after discontinuation of therapy. Maintenance therapy is guided by the patient's symptoms and his response to first-line treatments. Secondary therapies are used for maintenance therapy to reduce long-term steroid dose, or to replace successful TPE, or after failure of first-line therapies. Secondary therapies include azathioprine, cyclophosphamide, methotrexate, rituximab or alemtuzumab, cyclosporine, interferon-beta, and other immunosuppressives.

Rationale for therapeutic apheresis

The presumed etiology of CIDP is autoimmune attack on the peripheral nerves. Both humoral and cell-mediated immune responses have been documented. An increase in inflammatory cytokines has been observed in plasma and CSF. Complement activation might be associated with disease severity. The description of antibodies against gangliosides in acute and chronic inflammatory neuropathies, against myelin-associated glycoprotein (MAG) in monoclonal gammopathies, and against proteins of the paranode of Ranvier (Contactin-1, Contactin-associated-protein-1, Neurofascin-155) in CIDP highlights the importance of the humoral immune response, in particular autoantibodies, in the pathogenesis of CIDP. Utility of these autoantibodies as biomarkers with direct diagnostic, prognostic, and therapeutic implications needs to be further assessed.

Therapies are aimed at modulation of the abnormal immune response. In the first double-blind, sham-CT, patients who received TPE (average 47 mL/kg of plasma exchanged) versus sham plasma exchange twice weekly for 3 weeks demonstrated significant improvement (Dyck, 1986). In a randomized double-blind crossover trial, patients received 10 TPE (40-50 mL/kg plasma exchanged) or sham procedures over 4 weeks then a 5-week washout period and received 10 of the alternate procedure for 4 weeks: 80% had substantial improvement in their neurological function, of these 66% relapsed within 1-2 weeks, but responded to continued TPE (Hahn, 1996). In a randomized crossover trial of TPE (twice a week for 3 weeks then once a week for 3 weeks) versus IVIG (0.4 gm/kg once a week for 3 weeks then 0.2 gm/kg once a week for 3 weeks), both TPE and IVIG resulted in significant improvement and there was no significant difference between the two treatments (Dyck, 1994).

In a randomized pilot trial of TPE versus IA, patients received each 6 treatments with an equal plasma volume of 2.5 L per treatment. Both TPE and IA resulted in substantial clinical improvement in 44% versus 67% of patients (Lieker, 2017). In a retrospective study, IA was effective for select CIDP patients unresponsive to first-line treatment options, or for maintenance treatment avoiding regular replacement of human plasma products with their potential side effects or cost (Galldiks, 2011).

Technical notes

Volume treated: 1-1.5 TPV with TPE or IA	**Frequency:** 2-3/wk until improvement, then tapered, e.g. weekly or monthly
Replacement fluid: Albumin for TPE, none for IA	

Duration and discontinuation/number of procedures

TPE or IA provide short-term benefit, but rapid deterioration may occur afterwards. This may necessitate maintenance treatment, with repeated TPE, IA and/or other immunomodulating therapies, with frequency tailored to symptoms and tolerability of the individual patient.

Keywords: Chronic inflammatory demyelinating polyradiculoneuropathy, demyelinating neuropathy, plasma exchange, immunoadsorption

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COAGULATION FACTOR INHIBITORS

Incidence: Hemophilia A: 20-30%; Hemophilia B: 3-5%; Acquired FVIII inhibitor: <2/1,000,000/year; Inhibitors to other coagulation factors: rare		**Procedure**	**Recommendation**	**Category**
		TPE	Grade 2C	III
		IA	Grade 2B	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
TPE	0	0	9(98)	49(53)
IA	0	0	12(132)	NA

FVIII = factor VIII

Description of the disease

Coagulation factor inhibitors (antibodies) target specific coagulation factors leading to factor deficiency and potentially hemorrhage. Patients with moderate to severe congenital factor VIII or IX (FVIII or FIX) deficiency (hemophilia A and B, respectively) may make alloantibodies to exogenous factor replacement. This serious complication occurs in 20-30% and 3-5% of patients with hemophilia A and B, respectively.

Rarely patients without congenital factor deficiency make inhibitory antibodies that are autoantibodies, xenotropic alloantibodies following foreign factor exposure, or associated with plasma cell dyscrasia or myeloproliferative neoplasm (MPN). FVIII autoantibody development has a biphasic age distribution (small peak in women 20-30 years due to post-partum inhibitors and major peak in the elderly) with only approximately half of cases associated with a concomitant disease (e.g., pregnancy, malignancy, autoimmune disorder, infection, and medications). In acquired FVIII deficiency, hemorrhage tends to affect skin, muscle, soft tissue, and mucous membranes, rather than hemarthroses. Cross reactive xenotrophic alloantibodies against FV and prothrombin (FII) occurred in patients exposed to early formulations of bovine-derived fibrin glue. FV antibodies are associated with therapy with streptomycin, cefotaxime, tacrolimus, and infections (tuberculosis and HIV). Patients with lupus anticoagulants (LAC) may have selective FII autoantibodies and present with bleeding and concomitant antiphospholipid syndrome. Acquired von Willebrand syndrome (AVWS) may result from IgG or IgM antibodies that bind VWF and cause increased clearance or abnormal platelet adherence. Monoclonal proteins may also bind to coagulation factors leading to acquired deficiency or functional defects (laboratory assays of coagulation function may not accurately reflect the hemostatic derangement and bleeding risk). Systemic light chain amyloidosis is associated with acquired factor deficiency, most commonly reported with FX, due to selective binding to amyloid fibrils. In the case of FX deficiency laboratory measurements of coagulation function and FX activity levels are poor predictors of bleeding risk. Rare cases of inhibitors have also been reported for other coagulation factors, including FVII. FIX, FXI, FXIII, and protein S. Acquired protein S deficiency has been reported in some patients with varicella associated purpura fulminans.

The bleeding tendency with factor inhibitors is due to clearance of the specific factor and/or direct inhibition of factor function. Inhibitory antibodies are quantified and expressed as Bethesda units (BU); <5 BU is considered low titer.

Current management/treatment

Therapy for patients with coagulation inhibitors is based on diagnosis, presence of bleeding and inhibitor titer. Current treatment options for bleeding in patients acquired hemophilia A include high doses of FVIII, modified FVIII products, and FVIII bypassing factors, such as activated prothrombin complex concentrates and recombinant factor VIIa (rFVIIa). Treatment for suppression of inhibitor production may include several modalities. Based on European Acquired Haemophilia Registry (EACH2) data, approximately 70% of patients with acquired hemophilia A achieved complete remission with steroids plus cyclophosphamide (Collins, 2012). Treatment of patients with acquired FVIII inhibitors using the modified Bonn-Malmö protocol (IA, IVIG, cyclophosphamide, prednisolone, and FVIII), resulted in a 93% complete remission rate in the first year in patients without paraneoplastic syndromes (Zeitler, 2012). In congenital hemophilia A, immunologic tolerance can be induced by daily infusions of FVIII. Patients with acquired FV inhibitors have been treated treated with immunosuppression, IVIG and platelet and/or plasma transfusion. Patients with AVWS and hemorrhage are usually managed with desmopressin, antifibrinolytics, von Willebrand factor replacement therapy, activated prothrombin complex concentrates, IVIG or rFVIIa. Hypoprothrombinemia associated with LAC is treated with prothrombin complex concentrate and corticosteroids. MPN and plasma cell dyscrasias are treated as above to control bleeding, as well as treating underlying disorder.

Rationale for therapeutic apheresis

The extracorporeal removal of coagulation factor inhibitors with IA is better studied than TPE. CS and CRs indicate that IA can decrease antibody titers, improve the response of hemophiliacs to factor replacement, and decrease serious bleeding in patients with spontaneous inhibitors, but clinical response is not observed in all patients. Because IA requires special equipment that is not widely available and expensive, it is often reserved for patients with recalcitrant inhibitors who are unresponsive to other therapies.

TPE has been used to reduce inhibitor levels in patients with inhibitors to FVIII and several other coagulation factor inhibitors. Similar to IA, not all patients have responded to this therapy. CRs have conflicting results on the use of TPE in patients with systemic amyloidosis associated factor deficiency (see separate fact sheet). Small CS and CRs also describe the use of TPE to increase factor levels in patients without an inhibitor when a specific factor replacement product was unavailable or when the volume of simple plasma transfusion needed to reach target levels was greater than the patient would tolerate.

Changes from the 2016 ASFA evidence recommendation and category for this indication were based on the committee's review of past and recent literature and the effective use of TPE or IA for antibody removal in other conditions. The development of new products for treatment of patients with alloantibodies to FVIII and FIX may reduce the role of TPE or IA in these patients.

Technical notes

IA is a two-step procedure with plasma separation followed by plasma adsorption using plasma flow rates according to manufacturers' recommendations, generally in the range of 30-40 mL/min. Regenerative IA systems may be preferred in this patient group. Anticoagulant should be used at the lowest required amount.

Volume treated: TPE: 1-1.5 TPV; IA:2-3 TPV	**Frequency:** TPE: Daily; IA: Daily
Replacement fluid: TPE: Plasma; IA: NA	

Duration and discontinuation/number of procedures

Treatments are performed daily until bleeding is controlled with other therapeutic modalities.

Keywords: hemophilia, factor inhibitor, plasma exchange, immunoadsorption

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COMPLEX REGIONAL PAIN SYNDROME

Incidence: 6-26/100,000/yr	**Indication**	**Procedure**	**Recommendation**	**Category**
	Chronic	TPE	Grade 2C	III
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	2(39)	2(3)

Description of the disease

Complex regional pain syndrome (CRPS) is a debilitating disease associated with vasomotor, sudomotor, and sensory disturbances in an affected limb or region of the body. Patients with CRPS typically present with pain and prominent autonomic and inflammatory changes, such as extreme hyperalgesia and allodynia, skin color and temperature change, sweating, edema, and inhibited hair, skin, or nail growth. Patients can also have systemic symptoms involving organ systems, including respiratory, cardiovascular (tachycardia, orthostatic intolerance), gastrointestinal (dysmotility), and genitourinary (urinary retention), as well as generalized symptoms, like weakness and fatigue.

CRPS may be preceded by a traumatic event, such as fracture, soft tissue injury, or surgery. It occurs in 4-7% of patients with limb fracture or limb surgery. Although the majority of CRPS will resolve within weeks to months (acute CRPS), some may persist and become chronic (>1 year in duration). Patients with acute CRPS often have a warm, red, and edematous affected body region while patients with chronic CRPS patients have cold, dusky, sweaty areas with small fiber neuropathy seen in punch biopsy in some cases. CRPS is more common in women than in men, and association with HLA-DQ8 or HLA-B62 has been reported. CRPS may also occur in children, with lower extremity involvement and systemic dysautonomia reported. The pathophysiological mechanisms of CRPS are not fully understood, and autoantibodies against β2-adrenergic, α1-adrenergic, and muscarinic M2 receptors have recently been associated with this condition. Currently, there is no standard test for diagnosis; CRPS remains a clinical diagnosis of exclusion.

Current management/treatment

Chronic or severe CRPS is challenging to manage. Multidisciplinary approaches are generally used and recommended. Many therapeutic agents have been used with variable and often partial efficacy including bisphosphonates, gabapentin, calcitonin, intravenous ketamine, free radical scavengers, oral corticosteroids, and spinal cord stimulation. Due to the suspected auto-immune nature of the disease (in at least a subset of patients), steroids, IVIG, and rituximab have been tried and shown to have variable responses. Review of the published literature on the use of TPE in CRPS suggests that 38 out of 42 (90%) CRPS patients who underwent TPE (5 to 7 TPEs over 2 to 3 weeks) reported positive responses in terms of pain or improvement of other systemic symptoms. The majority required ongoing maintenance TPEs and/or immunosuppressive medications and adjunctive therapies to maintain symptomatic improvement. A recent RCT concluded that low-dose intravenous immunoglobulin treatment is not effective in relieving pain in patients with moderate to severe CRPS (Goebel, 2017).

Rationale for therapeutic apheresis

TPE can remove auto-antibodies to ß2-adrenergic, α1-adrenergic, and muscarinic M2 receptors (and possibly cytokines), and may relieve localized and systemic symptoms thorough this mechanism. The effect is likely transient. Maintenance TPE may be required, in combination with other therapies.

Technical notes

Volume treated: 1-1.5 TPV	**Frequency:** 5 to 7 TPEs over a 2 to 3-week period
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

As above, and then as indicated for maintenance management (as frequent as weekly).

Keywords: complex regional pain syndrome, plasma exchange

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CRYOGLOBULINEMIA

Incidence: About 50% of patients with chronic HCV	**Indication**	**Procedure**	**Recommendation**	**Category**
	Severe/symptomatic	TPE	Grade 2A	II
	Severe/symptomatic	IA	Grade 2B	II
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
TPE	1(57)	0	24(302)	NA
IA	1(17)	0	1(4)	0

Description of the disease

Cryoglobulins are immunoglobulins that reversibly precipitate below body temperature. The aggregates of cryoglobulins can deposit on small vessels and cause damage by activating complement and recruiting leukocytes. This most commonly occurs on the skin of lower extremities because of exposure to lower temperatures. End-organ complications range from minimal to severe. Cryoglobulinemia is associated with a wide variety of diseases including lymphoproliferative disorders, autoimmune disorders, and viral infections (e.g., hepatitis B and C). These disorders result in B cell proliferation possibly due to increase in BAFF (B cell-activating factor) or IgG-bound HCV driving clonal expansion. Mild symptoms include purpura, arthralgia, and sensory neuropathy. Severe end-organ effects include glomerulonephritis, neuropathy, and systemic vasculitis. When cryoglobulinemic vasculitis is present, the disease is referred to as CryoVas. Cryoglobulins are classified into three types: type I consist of monoclonal immunoglobulins, usually due to multiple myeloma (IgG) or Waldenström's macroglobulinemia (IgM), type II contains polyclonal IgG and monoclonal IgM rheumatoid factor usually due to HCV infection, and type III contain polyclonal IgG and IgM usually due to inflammatory disorders, autoimmune disease, or HCV infection. About 80-90% of individuals with mixed cryoglobulinemia (types II and III) have HCV. The diagnosis of cryoglobulinemia is made by history, physical findings, low complement levels, and detection and characterization of cryoglobulins (including quantitation by the cryocrit). There is no correlation between the severity of disease and cryocrit, however response to TPE was shown to be aligned with a measurable decrease in cryocrit. Individuals with type I have a higher cryocrit than individuals with type II or III.

Current management/treatment

Management is based on the severity of symptoms and treating the underlying disorder. Screening for infectious agents is critical in the setting of mixed CryoVas. Asymptomatic individuals do not require treatment of their cryoglobulinemia. Mild symptoms can be treated with cold avoidance and analgesics. More severe disease warrants the use of immunosuppressive therapy such as corticosteroids, cyclophosphamide, and rituximab. In a multicenter RCT, rituximab (1g IV at baseline and day 14) was compared with conventional treatment (corticosteroids plus azathioprine, cyclophosphamide, or TPE) in 59 patients with severe mixed CryoVas. Survival at 12 months was statistically higher in the rituximab group compared with conventional therapy (64% vs 4%, respectively). A large CS (CryoVas survey) demonstrated greatest therapeutic efficacy of rituximab plus corticosteroids over corticosteroids alone or with alkylating agents in patients with noninfectious mixed CryoVas (Terrier, 2012; 2015). A separate RCT in patients with severe HCV-associated CryoVas demonstrated statistically significant remission rates in patients in the rituximab group compared with conventional therapy (83% vs 8%, respectfully) (Sneller, 2012). HCV RNA levels were not affected by rituximab therapy. However more recent use of triple HCV therapy with PegIFN/ribavirin and a specifically targeted antiviral agent (NS3/4A protease inhibitor, i.e., boceprevir or telaprevir) has led to improved sustained virological response rates (65-70%) and are used for the treatment of cryoglobulinemia related to HCV genotype 1 infection. When cryoglobulinemia is associated with severe clinical manifestations such as skin ulcerations, glomerulonephritis or neuropathy, TPE has been used as an adjunct to control the symptoms by directly removing the cryoglobulins.

Rationale for therapeutic apheresis

TPE removes cryoglobulins efficiently with CRs and CS suggesting improvement in 70-80% of treated patients. It has been used mostly in active moderate to severe cryoglobulinemia with renal impairment (membranoproliferative glomerulonephritis), neuropathy, arthralgia and/or ulcerating purpura. TPE can be performed either alone or in conjunction with immunosuppressive therapy and has been used in both short- and long-term management.

Double or cascade filtration, which separates plasma out of whole blood in the first filter and removes high molecular weight proteins in the second filter (such as IgM), has also been used to treat cryoglobulinemia. Another apheresis modality used in this disease is cryofiltration or cryoglobulinapheresis, which cools the plasma in an extracorporeal circuit either continuously or in a 2-step procedure to remove cryoglobulins; the remaining plasma is warmed to body temperature prior to returning to the patient. Cryofiltration is less efficient at removing cryoglobulins than DFPP. In a randomized, parallel group study IA apheresis confirmed to be effective for lowering cryoglobulins (Stefanutti, 2009). This study was the lone RCT that included IA apheresis as in the intervention group in all 10 studies that met the selection criteria in a database systematic review (Montero, 2018).

Technical notes

It is prudent to warm the room, draw/return lines, and/or replacement fluid to prevent intravascular precipitation of the cryoglobulins. Precipitation of cryoglobulins in the extracorporeal circuit has been reported.

Volume treated: 1-1.5 TPV	**Frequency:** Every 1-3 Days
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

For acute symptoms, performance of 3-8 procedures, and re-evaluation for clinical benefit should be considered. TPE may rapidly improve acute symptoms and serve as a bridging therapy prior to treatment with immunosuppressive drugs. Weekly to monthly maintenance treatments may be indicated in patients who initially responded to TPE in order to prevent recurrent symptoms. Because the cryocrit is not a marker of disease activity, it should not be used as a criterion for initiating or discontinuing TPE.

Keywords: cryoglobulinemia, CryoVas, cryocrit, vasculitis, HCV, cryofiltration, immunoadsorption, plasma exchange

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CUTANEOUS T CELL LYMPHOMA (CTCL); MYCOSIS FUNGOIDES; SÉZARY SYNDROME

Incidence: MF: 6/1,000,000/yr; SS: 1/1,000,000/yr	**Indication**	**Procedure**	**Recommendation**	**Category**
	Erythrodermic MF/SS	ECP	Grade 1B	I
	Non-erythrodermic MF	ECP	Grade 2C	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Erythrodermic MF/SS	1(8)	4(64)	36(772)	NA
Non-erythrodermic MF	1(8)	2(18)	14(108)	NA

MF = mycosis fungoides; SS = Sézary syndrome

Description of the disease

Mycosis fungoides (MF) and its leukemic variant, Sézary syndrome (SS), account for 55% and 5% of cutaneous T cell lymphoma (CTCL) cases, respectively. Although both involve clonal (malignant) epidermotropic CD3+/CD4+ T cells, molecular studies and immunophenotypic analyses suggest that MF and SS evolve from different cells of origin. Diagnosis incorporates clinical, histopathologic, molecular and immunopathologic criteria. Disease staging evaluates skin, lymph node, visceral and blood involvement using TNMB criteria. Early stage MF (stage IA, IB, and IIA) can be challenging to diagnose. Stage I disease is limited to the skin with patches, papules or plaques (IA <10% body surface area [BSA]; IB ≥10%). Stage II indicates low grade lymph node involvement (IIA) or skin tumors (IIB). Erythrodermic MF is characterized by generalized erythroderma (≥80% BSA) alone (IIIA) or in the presence of a low burden (<5%) of clonal CD4+ T cells (Sézary cells) in the peripheral blood (IIIB). SS specifically denotes generalized erythroderma with nodal involvement and a high burden ($\geq 1 \times 10^9$/L) of circulating Sézary cells (IVA1). Disease with high grade lymph node (IVA2) or visceral involvement (IVB) is associated with very poor prognosis.

Current management/treatment

The treatment of MF/SS is usually palliative with therapy aimed at alleviating symptoms, improving skin manifestations, controlling extracutaneous complications and minimizing immunosuppression. Current skin directed treatment options include topical corticosteroids, topical mechlorethamine, topical bexarotene, ultraviolet phototherapy (PUVA or UVB), local radiotherapy and total skin electron beam therapy. Systemic therapies include retinoids (bexarotene, all-trans retinoic acid), interferon-alpha, chemotherapy (methotrexate, liposomal doxorubicin, gemcitabine), targeted immunotherapy (alemtuzumab, brentuximab), ECP, histone deacetylase inhibitors (vorinostat, romidepsin) and allogeneic stem cell transplantation. Treatment recommendations are based on stage (Trautinger, 2017). ECP is currently recommended as first line treatment, either alone or in combination with other skin directed or systemic therapies, for treatment of stage IIIA, IIIB and IVA1/SS disease and for maintenance after remission has been achieved.

Rationale for therapeutic apheresis

ECP involves leukapheresis, ex vivo treatment with 8-methoxypsoralen and UVA light, and subsequent reinfusion of the treated cells. Treatment induces apoptosis of malignant cells, which are phagocytosed by antigen presenting cells following reinfusion, and stimulates monocyte differentiation to myeloid dendritic cells with a Th1 phenotype that launch a cytotoxic response against the malignant clone. The overall response rate of CTCL to ECP is approximately 60% with complete response rates of 14-26%. Therapy with ECP correlates with short duration of disease, lower blood Sézary cell burden and significant early response of skin lesions (i.e., >50% regression within 6 months). ECP can be combined with systemic therapy such as retinoids and interferons for better response. ECP is not currently recommended for non-erythrodermic disease as it is thought to require blood involvement to be effective. However, there are CRs suggesting effectiveness and the National Comprehensive Cancer Network Guidelines lists ECP as a treatment option for refractory early stage disease. Advantages of ECP include the relative lack of immune suppression and lower risk of infections compared to systemic therapy.

Technical notes

One cycle (two daily ECP procedures) once or twice per month yields comparable results to more frequent or intensive photopheresis regimens. For patients with SS, two monthly cycles have been recommended.

Volume treated: Typically, MNCs are obtained from processing 1.5L of whole blood, but the volume processed may vary based on patient weight and HCT. The 2-process method collects and treats MNCs obtained from processing 2 TBV.

Frequency: Two consecutive days (one cycle) every 2-4 weeks. Benefit is not seen with more frequent treatments.

Replacement fluid: NA

Duration and discontinuation/number of procedures

The median time for a maximal response to ECP is 5-6 months although combination regimens may induce earlier remissions. Some patients may take as long as 10 months to respond. More rapid responses to ECP correlate with durability. Patients should be monitored and responses in skin, blood and lymph nodes documented as per published guidelines. When maximal response is achieved with ECP, it can be reduced to one cycle every 6-12 weeks with subsequent discontinuation if no relapses occur. If MF/SS recurs, ECP can be reinstituted at once or twice monthly. If there is no response or disease progression after 3 months of ECP alone, combination therapy or alternate agents should be considered.

Keywords: cutaneous T-cell lymphoma, Sezary syndrome, mycosis fungoides, extracorporeal photochemotherapy, cutaneous T cell lymphoma

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DILATED CARDIOMYOPATHY, IDIOPATHIC

Incidence: 36/100,000/yr (US)	**Indication**	**Procedure**	**Recommendation**	**Category**
	NYHA II-IV	IA	Grade 1B	II
	NYHA II-IV	TPE	Grade 2C	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
IA	4(109)	12(499)	NA	NA
TPE	0	1(7)	2(14)	2(2)

Description of the disease

Dilated cardiomyopathy (DCM) is characterized by progressive ventricular enlargement with impaired ventricular contractile function. Clinically patients present with signs and symptoms of congestive heart failure (dyspnea, orthopnea, impaired exercise tolerance, fatigue, and peripheral edema) and arrhythmias. Fifty percent of cases are idiopathic (iDCM). One third of iDCM cases result from inherited mutations in cytoskeleton proteins. The pathogenesis of the remaining iDCM cases appears to involve autoimmunity triggered by viral myocarditis. Viral genome can be detected on endomyocardial biopsy in up to 67% of patients with iDCM and 80% have autoantibodies toward various myocardial antigens (α-Myosin, β1-adrenergic receptor, Troponin-I, Na-K-ATPase, M2-muscarinic acetylcholine receptor).

Current management/treatment

iDCM is usually managed medically with angiotensin converting inhibitors, angiotensin receptor blockers, diuretics, digitalis, β-blockers, aldosterone antagonists, and vitamin K antagonists. Surgical management includes placement of a left ventricular assist device (LVAD) with the definitive therapy being cardiac transplantation. Treatment of iDCM with immunosuppression and/or IVIG has had mixed results.

Rationale for therapeutic apheresis

Most research to date on the application of apheresis in iDCM has examined the use of IA to remove cardiac autoantibodies. Trials and CS using IA columns have demonstrated short- and long-term clinical improvement as measured by echocardiography, invasive monitoring, oxygen consumption, exercise tolerance, oxidative stress markers, BNP levels, and standardized symptom assessments. Histologic improvements include decreased myocardial HLA expression, inflammation, and desmin gene expression. Factors associated with response to IA therapy have included shorter duration of disease, the presence of low immunoglobulin affinity Fcγ-receptor IIa polymorphisms, and greater impairment of left ventricular function.

One CT using anti-human polyclonal immunoglobulin (AHPI) IA in 34 patients found persistent reduction in β1-adrenergic receptor antibodies and improved left ventricular ejection fraction (LVEF) at 12 months with statistically significant differences in survival at 5 years between the treated group (82%) and matched controls (41%, $p < 0.0001$) (Muller, 2000). In addition to medical benefit, economic analysis found that the IA treatment was cost effective (Hessel, 2004). Another CT examined outcomes in 108 patients with β1-adrenergic receptor antibodies undergoing IA compared to 55 patients with antibodies who did not undergo IA and 19 patients without antibodies who underwent IA. The probability of being cardiac transplant or LVAD free at 5 years was 69% for those with antibodies who underwent IA treatment compared to 25% for those with antibodies who did not ($p < 0.05$). Patients who underwent IA but who lacked β1-adrenergic receptor antibodies had a 47% probability of being cardiac transplant or LVAD free at 5 years ($p < 0.05$) (Dandel, 2012). Data from 93 patients from the Berka registry support the positive effect of IA with subsequent IVIgG substitution in these patients (Ohlow, 2017). An RCT from Japan failed to reach the primary endpoint (radionuclide LVEF improvement) but showed significant improvements for echocardiographic LVEF, NYHA score and quality of life (Yoshikawa, 2016). In contrast to adults, only a few CS are available for pediatric patients (Moriguchi, 2017; Koizumi, 2017). These data seem to support that in children, as in adults, TPE treatment might be beneficial.

Based on a mixed response to apheresis treatment, investigators have searched for parameters that might predict response to IA (Bhardwaj, 2017; Ameling, 2016). Promising indicators include proteomic signatures and gene expression after IA, which might serve as predictors of who should be treated by IA. Patients with iDCM due to inherited cytoskeletal abnormalities have not been treated with IA and would not be expected to respond.

Technical notes

Studies have examined only optimally medically managed patients with symptoms for ≥6 months. IVIG (0.5 g/kg) was given after the last treatment in most IA studies and the TPE CS.

Four different IA columns (AHPI, Staphylococcal protein A agarose (SPAA), β1-adrenergic receptor antibody, and tryptophan polyvinyl alcohol) have been used. Clinical improvement and reduction in antibody levels are observed whether using columns specific for β1-adrenergic receptor antibody removal or nonspecific IA (Dandel, 2012). Comparison studies of IA columns found SPAA less effective due to a lower affinity for pathogenic IgG3 antibodies. Modified SPAA protocols with enhanced IgG3 removal were more effective. TPE has been used when IA was unavailable or when the extracorporeal volume of the IA device was too large for the patient being treated. The ideal apheresis system is not yet specified.

Volume treated: TPE: 1-1.5 TPV; IA: 2.5- 5L depending upon the saturation and regeneration characteristics of the column.	**Frequency:** TPE: 3-5 treatments - daily or every other day; IA: Various schedules: most commonly 5 treatments daily or every other day.
Replacement fluid: TPE: albumin; IA: NA	

Duration and discontinuation/number of procedures

An IA trial comparing treatment with a single course of 5 consecutive days to 4 courses of 5 consecutive days repeated every 4 weeks failed to demonstrate differences in LVEF at 3 and 6 months between the two treatment schemas. Repeat IA and TPE have been reported to be effective in

patients experiencing increasing β1-adrenergic receptor antibody titers and/or worsening LVEF. There is variability in schedules for IA. In some studies, repeated courses are used.

Keywords: dilated cardiomyopathy, idiopathic dilated cardiomyopathy, plasma exchange, immunoadsorption, plasmapheresis

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ERYTHROPOIETIC PROTOPORPHYRIA, LIVER DISEASE

Incidence: 2-5/1,000,000		**Procedure**	**Recommendation**	**Category**
		TPE	Grade 2C	III
		RBC Exchange	Grade 2C	III
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
TPE	0	0	1(3)	15(16)
RBC Exchange	0	0	1(3)	7(9)

Description of the disease

Erythropoietic protoporphyria (EPP) is a rare autosomal recessive disorder characterized by reduced activity of mitochondrial ferrochelatase, the final enzyme in the heme biosynthetic pathway. Most affected individuals are compound heterozygous for a common *FECH* low expression mutation (IVS3-48T>C) and a second loss-of-function *FECH* mutation; a few (<5%) have bi-allelic loss-of-function mutations. Ferrochelatase catalyzes insertion of ferrous iron into protoporphyrin to form heme. The enzyme deficiency results in the accumulation of metal-free protoporphyrin primarily in bone marrow reticulocytes, which can appear in the plasma and is taken up in the liver and is excreted in bile and feces. They are also found in circulating erythrocytes. An analogous phenotype results from gain-of-function mutations in the X-linked gene, *ALAS2*, the first enzyme in the heme synthetic pathway; this disease is termed X-linked protoporphyria (XLP). The diagnosis of EPP and XLP is based on demonstration of an increased level of erythrocyte total protoporphyrin and especially metal-free protoporphyrin. Erythrocyte total protoporphyrins levels show considerable inter-individual variation among patients with protoporphyria, depending at least in part on the severity of the underlying *FECH* or *ALAS2* mutations. Intraindividual variation is much less but may be as much as 20% over time in the absence of liver disease. Plasma porphyrins correlate roughly with erythrocyte levels but are much more variable over time, probably reflecting more rapid turnover. EPP and XLP both present with skin photosensitivity characterized by pain, redness, and itching within minutes of sunlight exposure in childhood. Protoporphyrin is lipophilic and poorly water-soluble; thus, the major means of excretion is by hepatic clearance and biliary excretion. Liver damage occurs in <5% of patients and has been attributed to precipitation of insoluble protoporphyrin in bile canaliculi and to protoporphyrin-induced oxidative stress. Should protoporphyric hepatopathy develop, levels of plasma and erythrocyte protoporphyrin and cutaneous photosensitivity can increase markedly, and the increased load of hepatotoxic protoporphyrin can accelerate liver damage. Patients with XLP or with EPP resulting from bi-allelic loss of function *FECH* alleles may have higher protoporphyrin levels from early in life and face a higher risk of hepatic complications.

Current management/treatment

Treatment of the photosensitivity in EPP and XLP patients consists mainly of preventing skin damage by avoiding light exposure (including utilizing yellow filters for some medical or surgical procedures), wearing protective clothing and barrier sunscreens. β-carotene which causes a mild skin discoloration may improve tolerance to sunlight in some patients. More recently, afamelanotide (EMA-approved in Europe but is yet to be FDA-approved), a melanocyte-stimulating hormone analogue, has been shown to reduce photosensitivity and increase the quality of life.

Early protoporphyric hepatopathy has the best chance of improvement. Once cholestasis is present, because of biliary blockage from protoporphyrin crystals, protoporphyric hepatopathy typically proceeds rapidly to fibrosis and liver failure. Early protoporphyric hepatopathy is treated with oral ursodiol to enhance protoporphyrin solubility in bile, and cholestyramine to interrupt the enterohepatic circulation of protoporphyrin. Additionally, oral antioxidants can be used (vitamin C, vitamin E, N-Acetyl Cysteine, green tea). Cholestatic liver failure in EPP and XLP is uncommon, often develops unexpectedly and can progress rapidly. Nonetheless, treatment recommendations are not supported by high quality studies. Hepatopathy impairs uptake and biliary excretion of protoporphyrin and causes marked further increases in plasma and erythrocyte porphyrin levels. The increase in erythrocyte levels may result in part from uptake of protoporphyrin from plasma. Current treatments, often used in combination, are directed at decreasing protoporphyrin production and the return of protoporphyrin to the liver via the enterohepatic circulation, enhancing protoporphyrin biliary excretion and its removal from the circulation by TPE. Transfusion to correct anemia can suppress erythropoiesis and the production of excess protoporphyrin. Hemin infusions may suppress protoporphyrin synthesis in the marrow or possibly in nonerythroid cells. Combination of treatments, such as transfusions, hemin, TPE, ursodeoxycholic acid and vitamin E are often applied, especially in patients with severe, rapidly progressive hepatopathy, and may achieve remission, or bridge patients to orthotopic liver transplantation (OLT), which can lower circulating porphyrins to levels that were present before hepatopathy developed, but does not correct the genetic deficiency and thus, does not address the continuing overproduction of protoporphyrin. Hematopoietic stem cell transplantation (HSCT) is curative for these disorders and can prevent recurrence of hepatopathy in the transplanted liver.

Rationale for therapeutic apheresis

The goal of TPE during acute protoporphyric liver failure is to decrease the protoporphyrin level in the plasma and to prevent further deposition in the liver; TPE may also remove bile acids with improvement in pruritus. Multiple sessions of TPE, in combination with intravenous hemin may be used. Some speculate that RBCs may serve as a sink to absorb excess plasma protoporphyrins, providing a rationale to consider RBC exchange to reduce plasma protoporphyrin levels; however, this remains of uncertain benefit. TPE alone or in combination with transfusions, hemin, ursodeoxycholic acid, and vitamin E is unlikely to reverse advanced-stage disease; however, many CRs support the potential benefits of these approaches to bridge patients prior to OLT or HSCT.

Technical notes

For RBC Exchange, the amount of required RBCs based on the desired post-procedure HCT (~35%) and fraction of the original red cells remaining (FCR, ~25-30%). Avoiding exposure of the patient to excess light during the procedure is recommended.

Volume treated: TPE: 1-1.5 TPV; RBC Exchange:1-1.5 RBC volume **Frequency:** TPE: Every 1-3 days; RBC Exchange: 3x/week

Replacement fluid: TPE: Albumin, plasma

Duration and discontinuation/number of procedures

Variable.

Keywords: Erythropoietic porphyria, erythropoietic protoporphyria liver, x-linked protoporphyria, porphyria, liver transplantation, RBC exchange, plasma exchange

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FAMILIAL HYPERCHOLESTEROLEMIA

Prevalence: Heterozygotes: 1/200-300; Homozygotes: 1-6/1,000,000	**Indication**	**Procedure**	**Recommendation**	**Category**
	Homozygotes	LA	Grade 1A	I
	Heterozygotes	LA	Grade 1A	II
	Homozygotes/Heterozygotes	TPE	Grade 1B	II
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
LA	4(207)	10(609)	NA	NA
TPE	0	1(10)	14(62)	NA

Description of the disease

Familial hypercholesterolemia (FH) is a common genetic cause of premature atherosclerotic cardiovascular disease (ASCVD) and comprises mutations in the genes encoding LDL receptor (LDLR), apolipoprotein B, proprotein convertase subtilisin-kexin type 9 (PCSK9), or LDLR adaptor protein 1. Patients with homozygous (HoFH) or compound heterozygous (c-HetFH) or HetFH represents a high-risk phenotype, or with established ASCVD a very high-risk phenotype. If left untreated patients with HetFH (LDL-C typically >190mg/dL [5mmol/L]) develop coronary heart disease (CHD) before age 55, while homozygotes (LDL-C typically >500mg/dL [>13mmol/L]) develop CHD early in life with an average mortality at 18 years. However, once diagnosed, lipid lowering treatment (LLT) is successful to attenuate development of atherosclerosis, prevent cardiovascular events, and reduce mortality in in all subgroups.

Current management/treatment

Reducing lifetime cardiovascular risk associated with accumulating cholesterol burden is the fundamental rationale for multimodal LLT in FH, which comprises lifestyle counselling, dietary restrictions, escalating combination drug therapy including PCSK9-inhibitors, and finally LA. A substantial number of HoFH patients, due to their mutational status, will not respond to PCSK9-inibitors. The number of HetFH candidates for LA may decrease, as more patients will be successfully treated by drug therapy. Lomitapide, an inhibitor of microsomal triglyceride transfer protein, or mipomersen, an apolipoprotein B antisense oligonucleotide have been approved for HoFH in the US, but due to side effects and cost their position in routine care remains unclear. Liver transplantation for HoFH-children can lead to striking improvement of hypercholesterolemia, but the risk of transplantation and long-term immunosuppression represent major concerns.

There is broad consensus that HoFH should be treated as early as possible, e.g., not later than age 8 years. Low body weight and vascular access represent challenges to initiating LA in small children. Current guidelines of targeted LLT for adult patients mention LDL-C targets <100mg/dL with high-risk, or <70 mg/dL with very high-risk. Differences exist between US and European guidelines.

Rationale for therapeutic apheresis

Extracorporeal elimination of lipoproteins started in 1975 using TPE, followed by the development of selective LA systems to avoid loss of beneficial plasma components and substitution of plasma products with regular treatment. Short-term effects of LA include improvement of myocardial and peripheral blood flow, and endothelial function. Regular extracorporeal LDL elimination reduced mortality in HoFH. A CT in HetFH patients demonstrated significant reductions in coronary events (Mabuchi, 1998). Long-term studies have demonstrated by imaging techniques stabilization or regression of coronary atherosclerosis. LA also alters atherogenic LDL subclass distribution and decreases inflammatory mediators. These results coupled with the randomized studies of LDL-C lowering drugs support that lowering LDL-C levels with LA remains a cornerstone to prevent progression of atherosclerosis and cardiovascular events in FH patients. LA can be safely continued or initiated during pregnancy.

LDL-C concentration follows a sawtooth like pattern during regular LA treatment. The Kroon formula is mostly referenced to calculate time-averaged LDL-C between two LA treatments adjusting for the non-linear rebound of LDL-C, and as surrogate parameter to evaluate the attainment of LDL-C target levels: $C_{ave} = C_{min}+0.73(C_{max}-C_{min})$, where C_{ave} = time-averaged LDL-C, C_{min} = LDL-C immediately after LA, C_{max} = LDL-C immediately prior to LA; Kroon, 2000). The equation was based on a cohort not receiving maximally tolerated LLT, thus probably overestimating the rebound velocity.

Cost-benefit considerations have a strong impact on how rigorous targeted LLT is implemented, and expensive novel drugs like PCSK9-antibodies, or LA as final step of escalating LLT are reimbursed. Substantial heterogeneity exists between countries regarding eligibility criteria for LA in reimbursement regulations using different LDL-C thresholds or additionally taking severity and progression of ASCVD into consideration, (e.g., the FDA lists >500 mg/dl for HoFH, >300 mg/dl for HetFH, and >100 mg/dl for HetFH with established CHD). Considering the linear relationship between LDL-C levels and the relative risk of major coronary events this appears mainly driven by awareness of, or availability of LA, and economic constraints. Therefore, actual practice of LA varies substantially between North America, European, and Asian countries. The availability of the selective LA systems and their superior efficacy in lipoprotein removal has made the use of TPE uncommon. TPE may be the only option in countries where selective LA systems are not available, or in small children where the extracorporeal volume of selective LA is too large.

Technical notes

Selective LA systems reduce LDL-C levels by >60-70% after a single session. For children with body weights of 10-20 kg, experiences with selective LA systems like plasma DSA or DFPP exist (Klaus, 2018). Priming the extracorporeal circuit with blood or plasma products might be considered. Angiotensin converting enzyme inhibitors are contraindicated with adsorption-based LA due to increased bradykinin generation, leading to profound hypotension. Monitoring of hemoglobin, ferritin, transferrin saturation is recommended along with iron supplementation for the prevention of anemia with long-term LA.

Volume treated: LA: treatment volumes vary according to recommendations of device manufacturers; TPE: 1-1.5 TPV.

Frequency: weekly or biweekly, adjusted by individual evaluation of LDL-C target attainment. FDA has recommended to obtain an inter-apheresis LDL-C level ≤ 120 mg/dL.

Replacement fluid: LA: NA; TPE: Albumin.

Duration and discontinuation/number of procedures

Indefinite regular treatment.

Keywords: familial hypercholesterolemia, LDL-cholesterol, lipoproteins, lipoprotein apheresis

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FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

Incidence: 7/1,000,000		**Indication**	**Procedure**	**Recommendation**	**Category**
		Recurrent in kidney transplant	TPE/IA	Grade 1B	I
		Recurrent in kidney transplant/ Steroid resistant in native kidney	LA	Grade 2C	II
		Steroid resistant in native kidney	TPE	Grade 2C	III
# reported patients: >300		**RCT**	**CT**	**CS**	**CR**
Recurrent in transplanted kidney	TPE	0	4(68)	50(628)	NA
	IA	0	0	8(56)	6(6)
Recurrent in transplanted kidney/ Steroid resistant in native kidney	LA	0	1(23)	6(112)	NA
Steroid resistant in native kidney	TPE	0	0	3(26)	4(4)

Description of the disease

The term focal segmental glomerulosclerosis (FSGS) is used to describe both a "clinical" disease characterized by primary podocyte injury, i.e., primary FSGS in most cases idiopathic, and a "pathologic" lesion (seen on microscopy) that occurs secondarily in many types of chronic kidney disease. FSGS is histologically characterized by focal areas of sclerosis of some glomeruli adjacent to other intact glomeruli. Several FSGS histological variants (cellular, collapsing, tip lesion, perihilar, and not otherwise specified) exist, which have different clinical presentations and treatment response. The majority (80%) of FSGS cases are idiopathic. Other causes include mutations in specific podocyte genes, secondary to drugs, and hemodynamic adaptive response. In many cases of primary FSGS, a plasma factor or factors of unknown origin are postulated that injure the filtration barrier and/or increase glomerular permeability. This hypothesis is supported by the observation that FSGS may recur in a renal allograft with a risk of 20-50% for first transplants, reaching 80-100% in repeated transplants. Soluble urokinase-type plasminogen activating receptor (suPAR) had been suggested as a major candidate for the circulating factor, however, with accumulating evidence this appears unlikely. The successful use of immunoadsorption techniques with various ligands demonstrates that putative circulating factors have immunoglobulin-like binding characteristics. Despite treatment, 30-60% of patients progress to end stage renal disease within 3-7 years. FSGS recurs in the renal transplant in 30-40% of patients. Idiopathic FSGS poses the highest risk of recurrence post-transplant. Other risk factors for recurrence are younger age, short duration of native kidney disease, history of recurrence with previous transplant, heavy proteinuria, bilateral native nephrectomy, race, and living donor kidney. FSGS recurrence can happen a few hours to 2 years post-transplant. If untreated, recurrent FSGS will ultimately lead to permanent graft loss within months. Those who lose grafts to recurrence have >80% chance of recurrent FSGS in subsequently transplanted kidneys.

Current management/treatment

Patients with primary FSGS developing nephrotic syndrome (proteinuria >3 g/day) are treated with corticosteroids as first-line therapy, followed by calcineurin inhibitors, and rituximab. Therapeutic apheresis may be considered if prior therapies have failed. For secondary FSGS, the underlying cause should be treated. The main goal of recurrent FSGS treatment is to achieve complete or partial remission of proteinuria and prevent premature allograft loss. TPE or IA is first-line therapy in recurrent FSGS and can result in partial or complete remission in >50% in children and adults. High dose corticosteroids, other immunosuppressives and/or angiotensin II receptor antagonists (ARB) or ACE inhibitors represent components of drug treatment. Rituximab, IVIG, and mycophenolate mofetil have also been used in conjunction with TPE.

Rationale for therapeutic apheresis

Patients with recurrent FSGS appear to have a circulating factor that increases glomerular permeability. Decreasing plasma concentration coincides with proteinuria improvement. Usually TPE is started once recurrence is diagnosed. The number of TPEs needed to control proteinuria, a surrogate marker of FSGS, is extremely variable. The overall reported remission rate is 50-70%. Delayed treatment initition (>2 weeks) appears to be more common in non-responders. Studies support the need for immunosuppression as well as continuing therapeutic apheresis. Some patients with recurrent FSGS have been treated with partial success with a combination of TPE and IA with staphylococcal protein A columns. In a recent trial using IA for early FSGS recurrence in 12 children, 10 were responders (Allard, 2018). The decrease of proteinuria occurred within the first 10 sessions after initiating IA. After 3 months of IA, 2 patients maintained remission without IA and 8 became IA dependent.

The rationale for use of LA in FSGS is based on the hypothesis that altered lipid metabolism in nephrotic syndrome resulting in hypercholesterolemia creates a lipotoxic environment affecting podocyte function (Raina, 2018). Experience is limited to CS and CRs. In the US, LA is FDA-approved for use in the treatment of adult and pediatric FSGS patients with nephrotic syndrome when standard treatment options, including corticosteroid and/or calcineurin inhibitors treatments, are unsuccessful or not well tolerated or in the post-transplant setting.

Technical notes

In addition to peripheral or central lines, vascular access may be obtained through arteriovenous fistulas or grafts used for dialysis.

Volume treated: TPE, LA, or IA with single use adsorbers: 1.0-1.5 PV; IA with regenerative adsorbers: 2-3 PV.	**Frequency:** Daily or every other day at initiation of treatment. Subsequent frequency and duration based on patient response.
Replacement fluid: TPE: Albumin, plasma; IA/LA: NA.	

Duration and discontinuation/number of procedures

One approach is to begin with 3 daily TPEs followed by at least 6 more TPEs in the subsequent 2 weeks, though other approaches have been reported. Proteinuria is the key parameter to evaluate and monitor response to treatment. Results with preemptive treatment have not been consistent. Tapering of apheresis treatment should be decided on a case by case basis and is guided by the degree of proteinuria. Timing of clinical response is variable and complete abolishment of proteinuria may take several weeks to months. Some patients require long-term regimens of weekly to monthly TPEs to prevent reappearance of the proteinuria. There are no clinical or laboratory characteristics that predict the likelihood of success with TPE. It is recommended that TPE be instituted as soon as recurrent FSGS is diagnosed, in order to halt the process and maintain kidney function. Considerations for IA treatment are essentially identical.

For LA a treatment schedule of 2/week for 3 weeks followed by 6 weekly treatments has been suggested. In the POLARIS study this resulted in a response rate of 54%, which was maintained in 48% after 2 years (Muso, 2015).

Keywords: plasma exchange, immunoadsorption, lipoprotein apheresis, focal segmental glomerulosclerosis, renal transplantation

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GRAFT-VERSUS-HOST DISEASE (GVHD)

Incidence: After allogeneic HSCT: 10-60% Grade II-IV aGVHD; 6-80% moderate-severe cGVHD	**Indication**	**Procedure**	**Recommendation**	**Category**
	Acute	ECP	Grade 1C	II
	Chronic	ECP	Grade 1B	II
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Acute	0	5(258)	16(315)	NA
Chronic	1(95)	6(163)	29(928)	NA

HSCT = hematopoietic stem cell transplant; aGVHD = acute GVHD; cGVHD = chronic GVHD

Description of the disease

Graft-versus-host disease (GVHD) remains a major cause of morbidity and mortality following hematopoietic stem cell transplant (HSCT). Classic aGVHD occurs before day 100 and manifests as inflammatory tissue injury and necrosis with skin and gastrointestinal (GI) tract inflammation and denudation, cholangiohepatic liver injury and cholestatic jaundice. Late aGVHD occurs after day 100 and is defined as signs and symptoms of aGVHD (+/- biopsy confirmation) without cGVHD. Late aGVHD is further subdivided into persistent, recurrent, or "de novo". Classic cGVHD typically affects skin, GI, liver, lungs, oropharynx, eyes, genital tract and/or musculoskeletal systems without aGVHD features and has distinctive or confirmatory diagnostic criteria. Overlap cGVHD occurs when concurrent aGVHD and cGVHD is present. Acute GVHD results from activation of donor T cells by host antigen-presenting cells (APCs), leading to T cell and cytokine-mediated tissue injury. Chronic GVHD is due to dysregulated allo- or autoreactive T cells, B cells, APCs and natural killer (NK) cells leading to fibrosis, inflammation, sclerosis and atrophy of affected tissues. Detailed clinical assessment and severity scores are developed to systematically grade GVHD subtypes.

Current management/treatment

Acute GVHD of grades II-IV is treated with corticosteroids and calcineurin inhibitors. Fifty percent of patients will not completely respond and other immunosuppressive therapy or ECP will be required as salvage treatment. Moderate to severe cGVHD is managed with corticosteroids with or without other systemic immunosuppressive therapies. Treatments for steroid-refractory (SR) or -dependent (SD) extensive cGVHD include other immunosuppressive therapies and ECP.

Rationale for therapeutic apheresis

ECP works through ex vivo 8-methoxypsoralen and UVA treated lymphocytes, which, when returned to the patient, undergo apoptosis and modulate in vivo immune responses (increased dendritic cell differentiation, down regulation of autoreactive B cells, alterations in T helper subset populations and lymphocyte homing antigen display, switch from proinflammatory to anti-inflammatory cytokine production, and generation of regulatory T cells). Overall response rates for SR aGVHD reportedly range from 52-100%; with responses in 66-100% for skin, 40-83% GI tract and 27-71% in liver. A multicenter comparative analysis of ECP ($n = 57$) versus anticytokine therapy with inolimumab or etanercept ($n = 41$) as a second line treatment for SR aGVHD reported higher overall response in the ECP group (66% vs. 32%, $p = 0.001$) along with a significant survival advantage for patients receiving ECP (Jagasia, 2013). Complete responses and improved survival are often reported among aGVHD cohorts; however, the results for ECP are not superior to results reported for alternative salvage approaches for SR aGVHD. Several authors have suggested an earlier use of ECP in the acute phase of inflammation to improve complete response rate.

ECP for cGVHD has variable response rates. A systematic review looking at cGvHD showed pooled response rate for skin, liver, ocular, oral, lung, GI and musculoskeletal SR cGvHD was 74%, 68%, 60%, 72%, 48%, 53% and 64%, respectively (Malik, 2014). To date the only RCT using ECP for SR skin cGVHD observed no statistically significant difference in total skin score at 12 weeks of ECP plus salvage therapy, compared to salvage therapy alone. However, non-blinded assessments recorded 40% complete and partial response in the ECP compared to 10% in the non-ECP group and corticosteroids were able to be more quickly tapered in the ECP group (Flowers, 2008). A follow-up crossover randomized study after a 24-week course of ECP showed objective responses in skin (33%) and extracutaneous tissue (up to 70%) suggesting prolonged ECP is necessary for optimal therapeutic effect (Greinix, 2011). Maximal responses for cGVHD require 2-6 months of treatment. Many clinical practice guidelines and consensus statements addressing the use of ECP for GVHD have been published and, collectively, consider ECP as an established second-line therapy option for SR cGVHD. Importantly, steroid sparing effect occurs, even in absence of organ improvement, and therefore improves quality of life.

Preliminary reported results suggest that ECP may effectively improve/slow lung function decline in cGVHD patients with bronchiolitis obliterans syndrome (BOS) after standard treatment failure. Some authors recommend consideration of ECP as adjunctive first-line modality for GVHD associated BOS. Further studies are needed to confirm the efficacy of ECP, assess the optimal schedule and consider it for early treatment.

Technical notes

Inline/closed methods (all steps are performed in one system), offline systems (leukapheresis system for MNC collection and a separate illumination system), and Mini ECP (manual MNC preparation from whole blood with a separate illumination system) are used for ECP. Two treatments (typically on consecutive days) in 1 week are often designated 1 cycle.

Volume treated: Typically, MNCs are obtained from processing 1.5L of whole blood, but volume processed varies based on patient weight, HCT, and method utilized. 2-process method collects and treats MNCs obtained from processing 2 TBV.

Frequency: aGVHD: 2-3 treatments weekly, tapering to 2 treatments every 2 weeks; cGVHD: 2 treatments weekly for 4 weeks then 2 treatments every 2 weeks for at least 8-12 weeks for response assessment

Replacement fluid: NA

Duration and discontinuation/number of procedures

For aGVHD, one cycle performed weekly until disease response and then tapered to every-other-week before discontinuation. For cGVHD one cycle weekly for 4 weeks (or consider biweekly if treating only mucocutaneous cGVHD) and then one cycle every 2 weeks or for at least 8 weeks (assess at 2-3 monthly intervals), continue to maximum response every 2-4 weeks with taper.

Keywords: acute graft versus host disease, bronchiolitis obliterans syndrome, chronic graft versus host disease, extracorporeal photochemotherapy, photopheresis

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HEMOLYSIS, ELEVATED LIVER ENZYMES, AND LOW PLATELETS SYNDROME (HELLP SYNDROME)

Incidence: <1% of all pregnancies, 10-20% of pregnancies with pre-eclampsia	**Indication**	**Procedure**	**Recommendation**	**Category**
	Postpartum	TPE	Grade 2C	III
	Antepartum	TPE	Grade 2C	IV
# reported patients: 100-300	**RCT**	**CT**	**CS**	**CR**
	0	1(55)	7(127)	NA

Description of the disease

The HELLP syndrome (Hemolysis, Elevated Liver enzymes and Low Platelets) is a peripartum thrombotic microangiopathic syndrome characterized by hemolysis, low platelets and liver dysfunction. HELLP typically presents in the 3rd trimester of pregnancy but up to ¼ of patients may present post-partum. In 70-80% of cases, HELLP coexists with pre-eclampsia but can also occur in the absence of hypertension or proteinuria. Patients with severe HELLP may develop disseminated intravascular coagulopathy (DIC), and multi-organ failure. Other clinical entities that can present with similar features include immune thrombocytopenia, thrombotic thrombocytopenia purpura (TTP), hemolytic uremic syndrome, antiphospholipid syndrome, systemic lupus erythematosus, acute fatty liver of pregnancy and HELLP-like conditions caused by severe hypovolemic shock, sepsis, and sickle cell crisis. In contrast to TTP, ADAMSTS-13 levels in HELLP are typically low but detectable (20-50%). Autoantibodies against ADAMTS13 are not present in HELLP. The pathogenesis remains incompletely understood but is currently thought to result from endothelial dysfunction and an inflammatory response that leads to thrombotic microangiopathy (TMA). Diagnosis is based on the presence of TMA (as evidenced by elevated lactate dehydrogenase [LDH], indirect hyperbilirubinemia, and schistocytes on peripheral smear), thrombocytopenia, and elevated liver enzymes. Women who develop HELLP have a high risk of recurrence in subsequent pregnancies (14-24%).

Current management/treatment

Prompt delivery by cesarean section is the definitive treatment for HELLP. Prolongation of pregnancy has been associated with increased maternal and perinatal mortality. Steroids are used to support fetal lung maturity in pre-term cases. Some centers routinely use high dose steroids, but this practice remains controversial as two meta-analyses showed improvement in laboratory studies, but no benefit for maternal morbidity or perinatal death. Additional supportive therapies include hypertension management, parental magnesium therapy for seizure prophylaxis, and management of complications.

Rationale for therapeutic apheresis

TPE is speculated to remove circulating protein bound platelet aggregating and procoagulant factors released from both activated platelets and endothelial cells. Multiple CRs, CS and one retrospective CT (Eser, 2005) have shown clinical benefit of TPE in severe post-partum HELLP along with clinically significant improvement in platelet counts and decreases in serum LDH and aspartate aminotransferase levels. TPE is utilized when there is a failure of the patient to improve within 48-72 hours following delivery. Although TPE seems to confer benefit when applied to severe post-partum cases, many studies were done without ADAMTS-13 measurements to rule out TTP and may have included patients who had TTP. TPE is the primary therapy for TTP and should be initiated when there is clinical suspicion of TTP (see separate fact sheet). One small study which used ADAMTS-13 levels to differentiate HELLP from TTP showed recovery in 4 severe HELLP cases treated with high dose steroids without the use of TPE (Pourrart, 2013). There is no role for TPE in ante-partum HELLP as treatment may delay delivery, the definitive treatment for HELLP.

Technical notes

Volume treated: 1-1.5 TPV	**Frequency:** Daily if there is no improvement at 48-72 hours after delivery
Replacement fluid: Plasma	

Duration and discontinuation/number of procedures

TPE in post-partum HELLP is generally performed until platelet counts are >100×10^9/L or LDH has normalized.

Keywords: HELLP syndrome, hemolysis, elevated liver enzymes, low platelets, pregnancy, thrombotic microangiopathy, plasma exchange

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HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH); HEMOPHAGOCYTIC SYNDROME; MACROPHAGE ACTIVATING SYNDROME

Incidence: 1/800,000/yr (adults)); 1/1,000,000/yr (children)		**Procedure**	**Recommendation**	**Category**
		TPE	Grade 2C	III
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	1(23)	2(8)	8(9)

Description of the disease

Hemophagocytic syndrome or Hemophagocytic lymphohistiocytosis (HLH) is an immune-mediated life-threatening disease. It is caused by impaired natural killer and cytotoxic T cell function, which can be either primary (genetic, familial hemophagocytic lymphohistiocytosis [FHLH]) or secondary (reactive) after viral (EBV, CMV, H1N1, H5N1, parvovirus B19, influenza), bacterial (tuberculosis, *Rickettsia spp., Staphylococcus spp., E.coli*), or fungal and parasitic infections (histoplasmosis, malaria, toxoplasmosis, pneumocystis pneumonia), cancer, vaccinations, surgery, gravidity or autoimmune diseases (macrophage activating syndrome [MAS] in rheumatic disease). This results in an acute cytokine storm triggering an avalanche of hyper-inflammation with a severe sepsis like clinical picture. This hyperinflammation leads to a life threating clinical picture with disseminated intravascular coagulopathy (DIC), organ failure, pancytopenia, systemic immune response syndrome (SIRS) and potentially death, if untreated, in a few weeks. The diagnosis should be suspected in patients presenting with unexplainable, continuous high fever, and evidence of multiple organ involvement. Diagnosing HLH can be challenging. Hence, diagnostic guidelines from the Histiocyte Society are widely used. This guideline defines HLH by the presence of at least five of the following eight criteria: (1) fever, (2) splenomegaly, (3) bicytopenia, (4) hypertriglyceridemia and/or hypofibrinogenemia, (5) infiltration with lymphocytes and histiocytes of, and hemophagocytosis in bone marrow, spleen, lymph nodes, or liver, (6) low/absent NK cell activity, (7) hyperferritinemia, and (8) high-soluble interleukin-2 receptor (CD25) levels. Molecular diagnoses consistent with FHLH are mutations in *PRF1, UNC13D, STXBP1, RAB27A, STX11, SH2D1A,* or *XIAP.* Macrophage activation syndrome (MAS) is characterized by uncontrolled activation and proliferation of T lymphocytes and macrophages and is classified among secondary forms of HLH.

Current management/treatment

The basis of treatment of HLH are supportive intensive care according to the standards for similar life-threatening diseases, the elimination of the trigger (for example rituximab in EBV associated HLH after HSCT] and the suppression of inflammatory response and cell proliferation or both with immunosuppressive and cytotoxic drugs (cyclosporine, corticoids, etoposide, IVIG, alemtuzumab). For FHLH in pediatric patients, HSCT is a curative option after immunosuppressive therapy with corticosteroids, cyclosporine and etoposide. Data from retrospective studies show encouraging treatment response of secondary HLH with corticosteroids and IVIG, both alone and in combination with etoposide, cyclosporine, and alemtuzumab. In life threatening situations with uncontrolled hemorrhage and infections risk due to DIC and granulocytopenia and thrombocytopenia plasma, activated recombinant FVII, and cytokines (G-CSF) have been used. Extracorporeal treatments like TPE have been used for supportive care to stabilize organ function.

Rationale for therapeutic apheresis

The rationale for use of TPE in HLH includes removal of toxic substances as a result of organ failure (particularly liver failure) and suppression of the hyperinflammatory syndrome secondary to cytokine storm. In children with HLH one CT has been performed to date. Twenty-three children with hyperferritinemia and secondary HLH/sepsis/MODS/MAS were enrolled (median number of organ failures per patient was 5). The study demonstrated that use of TPE and methyl prednisolone or IVIG therapy (n = 17, survival 100%) was associated with improved survival compared to TPE and dexamethasone and/or cyclosporine and/or etoposide (n = 6, survival 50%; p = 0.002) (Demirkol, 2012). A comprehensive review of outcomes in adult HLH patients showed that those who received TPE had a survival rate of nearly 77% (20/26; survival of patients with cancer 9/10, autoimmune disease 6/8, infection 5/7, idiopathic 0/1) (Ramos-Casels, 2014). CRs suggest efficacy of TPE in HLH-associated liver failure.

Technical notes

Filtration systems and centrifugal systems have been used. There is no clear advantage of one technique over the other.

Volume treated: 1-2 TPV	**Frequency:** Daily, based on therapeutic goals
Replacement fluid: Albumin, plasma	

Duration and discontinuation/number of procedures

Heterogeneity of patient presentations and severity complicate determination of duration and intensity of procedures. TPE use should be tailored to local intensive care practice and clinical status of the patient.

Keywords: Hemophagocytic lymphohistiocytosis, hemophagocytic syndrome, familial lymphohistiocytosis, macrophage activating syndrome, plasma exchange, plasmapheresis

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HEPARIN-INDUCED THROMBOCYTOPENIA AND THROMBOSIS (HIT/HITT)

Incidence: <5% of patients exposed to heparin	**Indication**	**Procedure**	**Recommendation**	**Category**
	Pre-CPB	TPE	Grade 2C	III
	Thrombosis	TPE	Grade 2C	III
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
Pre-CPB	0	0	2(15)	9(10)
Thrombosis	0	1(44)	1(4)	6(6)

CPB = cardiopulmonary bypass

Description of the disease

Heparin-induced thrombocytopenia and thrombosis (HIT/HITT) is a major cause of morbidity and mortality in patients receiving heparin. Thrombocytopenia classically begins 5-10 days after heparin exposure, although individuals with a recent heparin exposure (generally within the preceding 100 days) may rapidly develop thrombocytopenia (within 24 hours) upon heparin re-exposure. Thrombosis typically affects large vessels, with venous events more common than arterial. A 5-year epidemiological study of HIT patients in the US observed a thrombosis rate of ~30% and a mortality rate of ~10% (Dhakal, 2018). Delayed-onset HIT (HIT that begins or worsens after stopping heparin) is often recognized because of thrombosis and is associated with a higher frequency of overt disseminated intravascular coagulopathy (DIC) and risk of microvascular thrombosis. Cases of spontaneous HIT have been reported where the clinical and serological picture is consistent with HIT, but the patient has no known heparin exposure within the preceding weeks. Clinical scoring tools are helpful for the risk assessment of HIT, with the 4Ts scoring system the most widely utilized. Antibodies specific for platelet factor 4 (PF4) and heparin complexes are a hallmark of HIT and several immunological and functional assay are used to identify these antibodies.

Current management/treatment

The first step in management of HIT is discontinuation of all heparin, including flushes and heparin coated devices. Because of the continued risk of thrombosis after heparin cessation, all patients with confirmed or strongly suspected HIT should be treated with nonheparin anticoagulants, such as the direct thrombin inhibitors (DTI) argatroban and bivalirudin; fondaparinux; or danaparoid; however, the last two are not FDA approved for patients with HIT and danaparoid is unavailable in the US. Limited CS and CRs have reported use of direct oral anticoagulants in patients with HIT. Management is particularly challenging in two scenarios: 1) worsening or new thrombosis with life- or limb-threatening complications despite optimal management with nonheparin anticoagulants; and 2) persistent platelet-activating HIT antibodies in patients who need emergent/urgent cardiac surgery on cardiopulmonary bypass (CPB). The standard anticoagulant used with CPB is unfractionated heparin (UFH) due to its longstanding track record of use in this setting, its short half-life, and immediate reversibility; however, UFH is typically contraindicated in patients with acute or subacute HIT (persistent platelet-activating HIT antibodies without thrombocytopenia). In this setting, consensus guidelines recommend the use of bivalirudin over other non-heparin anticoagulants and over heparin plus antiplatelet agents. The major concern with DTI use in CPB is severe bleeding due to lack of reversibility. IVIG has also been used in severe cases.

Rationale for therapeutic apheresis

In the setting of CPB with a prior history of HIT but no detectable HIT antibodies, brief UFH anticoagulation during CPB is usually well tolerated. In the setting of urgent need for surgery with CPB during acute or subacute HIT, TPE may be considered prior to CPB with UFH, as an alternative to using a DTI, during bypass. In the largest retrospective CS on the use of TPE in the pre-CPB setting, in 9 evaluable patients a single TPE treatment reduced HIT antibody titers (as measured by PF4-polyvinylsulfonate immunoassay) to negative (<0.4 OD) in 6 patients and significantly decreased titers in 3 patients (decreased 48-78%) (Welsby, 2010). None of the 9 patients developed clinical HIT after CPB with UFH; however, one patient developed a non-HIT related ischemic foot. A single CR suggests IVIG, without TPE, may also be effective when given pre-CPB (Warkentin, 2018).

TPE has also been used in the setting of life- or limb-threatening new or progressive thrombosis in HIT patients. In the largest study of TPE in HIT patients with severe thrombosis, three experimental patient groups were compared: 1) the “early” group (n = 21) received TPE within 4 days of onset of thrombocytopenia; 2) the “late” group (n = 7) received TPE 4 days or later after onset; and 3) the control group (n = 16) did not receive TPE. Reduction in HIT antibody levels was quantified by optical density in a PF4-heparin immunoassay or heparin-induced platelet aggregation (HIPA). TPE treatment resulted in a negative HIPA test in >75% of all patients tested by this method. The 30-day mortality rate was 5%, 57% and 32% in the early, late and control groups, respectively. Platelet recovery time, incidence of thrombotic events, and length of hospital stay were similar in the early group and controls but were longer/higher in the late group (Robinson, 1999). CRs have also described the use of TPE in patients with persistent thrombocytopenia.

Technical notes

TPE results in a rapid decrease in platelet-activating HIT antibodies, as determined by the serotonin release assay (SRA) even in the presence of strongly reactive antibodies detected by HIT immunoassays (Warkentin, 2015). While platelet activation assays, such as the SRA, are thought to measure clinically-relevant antibodies and thus may be more helpful in guiding TPE treatment in patients with HIT, these assays may be insensitive for detection of some platelet-activating antibodies. While both albumin and plasma have been used for TPE, *in vitro* data suggests IgG containing plasma may be more effective than albumin in inhibiting HIT antibody-mediated platelet activation (Jones, 2018).

Volume treated: 1 -1.5 TPV	**Frequency:** Daily or every other day
Replacement fluid: Albumin, plasma	

Duration and discontinuation/number of procedures

In the setting of CPB, TPE has been used preoperatively until HIT antibody titers become negative by the testing method used. In the setting of thrombosis, the number of procedures performed has been heterogeneous (1-5) and guided by clinical response (e.g., resolution of thrombosis-related tissue ischemia or thrombocytopenia, reduction in HIT antibodies level).

Keywords: Heparin induced thrombocytopenia and thrombosis, heparin induced thrombocytopenia, cardiopulmonary bypass, serotonin release assay, direct thrombin inhibitors, plasma exchange, thrombosis

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HEREDITARY HEMOCHROMATOSIS

Incidence: 1-2/100,000/yr		**Procedure**	**Recommendation**	**Category**
		Erythrocytapheresis	Grade 1B	I
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	3(146)	2(98)	13(122)	NA

Description of the disease

Hereditary hemochromatosis (HH) includes several inherited disorders that result in iron deposition in the liver, heart, pancreas and other organs. The genetic mutation, accounting for >90% of cases (and almost all cases in Caucasians of Northern European ancestry) is homozygosity for a single missense mutation in *HFE* on chromosome 6p21 that results in substitution of cysteine with tyrosine at amino acid 282 (C282Y), known as type I HH. The prevalence of type I HH is approximately 1:200 among Caucasians. Abnormalities of *HFE* result in abnormal iron sensing in the deep crypt cells of gut epithelium and thus inappropriate iron uptake despite abundant iron stores in the body. Other genetic mutations coding for hemojuvelin (*HFE2*, type IIA), hepcidin (*HAMP*, type IIB), transferrin receptors (*TFR2*, type III) or ferroportin (*SLC40A1*, type IV), have been described in rare families with non-HFE HH. In HH, iron accumulation can ultimately result in liver failure (cirrhosis, hepatocellular carcinoma), diabetes, hypogonadism, hypopituitarism, arthropathy, cardiomyopathy and skin pigmentation. Diagnosis is suggested by a persistent serum transferrin saturation of ≥ 45% and/or unexplained serum ferritin of ≥300 ng/mL in men or ≥200 ng/mL in premenopausal woman. The clinical penetrance of disease is variable, with only 70% of homozygotes developing clinical manifestations of disease, only 10% any end-organ complications, and <1% full-blown complications.

Current management/treatment

Because HH is a disease of iron overload, iron removal by therapeutic phlebotomy has been the mainstay of treatment both to remove iron and to increase erythropoiesis to mobilize stored iron. Phlebotomy is recommended when serum ferritin is elevated even in the absence of symptoms or signs of end-organ damage. Typically, 1 whole blood unit is removed weekly or biweekly until the serum ferritin is <50 ng/mL without resultant anemia. Patients with tissue complications of hemochromatosis usually have a ferritin >1000 ng/mL and present with upward of 20 gm of excess iron. Thus, with 250 mg of iron removed per phlebotomy, two years may be needed to achieve therapeutic iron depletion. Thereafter 2-4 phlebotomies per year are usually adequate to maintain the ferritin ≤50 ng/ml. Malaise, weakness, fatigability and liver transaminase elevations often improve during the first several weeks of treatment, but joint symptoms may initially worsen before eventually improving (if at all). Cardiomyopathy and cardiac arrhythmias may resolve with phlebotomy, but insulin-dependent diabetes generally will not. The risk of hepatocellular carcinoma correlates strongly with cirrhosis and persists despite iron depletion. In situations where therapeutic phlebotomy is contradicted, iron chelation can be used as an alternative treatment, although it is costly and has side effects.

Rationale for therapeutic apheresis

An RCT compared biweekly erythrocytapheresis of 350-800 ml of RBCs to a minimum post-procedure Hct of ≥30% with weekly phlebotomy of 500 mL among 38 patients with newly diagnosed HFE HH. The mean number of procedures and treatment duration to achieve ferritin of ≤50 ng/mL were 9 and 20 weeks for the erythrocytapheresis group versus 27 and 34 weeks ($p < 0.001$ and $p < 0.002$), respectively, for the phlebotomy group. No difference in adverse events and no significant difference in total treatment costs were observed (the higher cost of erythrocytapheresis was offset by a significant reduction in lost work productivity due to phlebotomy visits) (Rombout-Sestrienkova, 2012). A second RCT enrolled 30 patients for biweekly apheresis (400 mL) and 32 patients for weekly whole blood phlebotomy (450 ml). Time to normalization (50ng/mL) of ferritin was equivalent; cost for apheresis was 3x higher in this study (Sundic, 2014). A CT using another apheresis platform removed 300-550 ml of RBCs in patients with Hct >37%, weight >50 kg and age 18-65 years with mean reduction of 405 mg of iron per procedure (Grabmer, 2015). A crossover clinical trial randomized 46 HH patients to either erythrocytapheresis or phlebotomy to keep ferritin at 50 μg/L or below for one year and then switched groups (Rombout-Sestrienkova, 2016). In this study, mean number of procedures per treatment year was significantly higher using phlebotomy versus erythrocytapheresis (3.3 vs. 1.9; mean difference, 1.4; 95% confidence interval, 1.1-1.7). The median intertreatment time was 2.3 times longer for erythrocytapheresis. Eighty percent of the patients expressed preference for the erythrocytapheresis over phlebotomy. The cost and ability to rapidly lower ferritin and iron stores differ by the ability of RBC reduction per apheresis procedure, which varies by apheresis technology, and patient's weight and height. The reduction in the number of required procedures per year to maintain a goal ferritin level may give a cost benefit of erythrocytapheresis over phlebotomy.

Technical notes

The volume removed and pre-procedure HCT vary by height, bodyweight and gender. The actual volume of erythrocytes to be removed (VR) with each procedure can be calculated as:

$$VR = [(\text{starting HCT - target HCT}) \div 79] \times [\text{blood volume (mL/kg)} \times \text{body weight (kg)}].$$

Volume treated: Erythrocytapheresis of up to 800 ml of RBCs	**Frequency:** Every 2-3 weeks, keeping the pre-procedure HCT ≥30-36% and post-procedure HCT ≥30%
Replacement fluid: Replace at least ⅓-½ of removed RBC volume with saline	

Duration and discontinuation/number of procedures

Erythrocytapheresis every 2-3 weeks, or as tolerated, until serum ferritin <50 ng/mL. Maintenance treatment can follow with less frequent therapeutic phlebotomy or erythrocytapheresis.

Keywords: hemochromatosis, erythrocytapheresis, phlebotomy

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HYPERLEUKOCYTOSIS

Incidence: AML: WBC >100×10⁹/L; 5-13% adults; ALL: WBC >400×10⁹/L; 10-30% adults	**Indication**	**Procedure**	**Recommendation**	**Category**
	Symptomatic	Leukocytapheresis	Grade 2B	II
	Prophylactic or secondary	Leukocytapheresis	Grade 2C	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
AML	0	14(2400)	NA	NA
ALL	0	6(578)	NA	NA

AML = acute myeloid leukemia; ALL = acute lympoblastic leukemia

Description of the diseas

Hyperleukocytosis is typically defined as a circulating white blood cell (WBC) >100 × 10^9/L. In AML, it usually associates with myelomonocytic or monocytic leukemia or the microgranular variant of acute promyelocytic leukemia (APL). In ALL, it associates with male gender, T cell phenotype, infants, and patients ages 10-20 years. Patients with hyperleukocytosis may also present with tumor lysis syndrome (TLS), disseminated intravascular coagulopathy (DIC), and leukostasis, which is characterized by clinical evidence of decreased tissue perfusion and if unrecognized, the 1-week mortality can be as high as 40%. Leukostasis is diagnosed clinically using a grading system (Novotny, 2005). Central nervous system manifestations include confusion, somnolence, dizziness, headache, coma, and parenchymal hemorrhage. Pulmonary complications include hypoxemia, diffuse alveolar hemorrhage, and respiratory failure. Priapism may also occur. The pathogenesis is unclear, but may relate to cell rigidity, size, rheological properties, high metabolic activity causing local hypoxia, cytoadhesive interactions, and endothelial damage. Compared to lymphoid blasts, myeloid blasts are larger, less deformable, and their cytokine products are more prone to activate inflammation and endothelial cell adhesion molecule expression. Thus, in AML patients, leukostasis can occur when WBC >100 × 10^9/L while in ALL, it is rarer and may not occur until WBC >400 × 10^9/L (Giammarco, 2017). Importantly, it can occur in myelomonocytic and monocytic subtypes when WBC >50 × 10^9/L. Leukostasis complications with other leukemias are rare but may occur with chronic myelomonocytic leukemia when the WBC count exceeds 100 × 10^9/L with high LDH.

Current management/treatment

Definitive treatment of hyperleukocytosis involves induction chemotherapy with aggressive supportive care, including TLS prophylaxis. Hydroxyurea and/or cytarabine are useful temporizing cytoreductive agents for AML. Rapid cytoreduction is indicated for symptomatic leukostasis. Although hyperleukocytosis in AML is associated with a 2- to 3-fold higher early mortality rate, the relative benefits of rapid cytoreduction by leukocytapheresis versus aggressive chemotherapy and supportive care alone remains poorly defined. CML during pregnancy can be treated with interferon-γ safely during the second and third trimester. The threshold to perform leukocytapheresis in asymptomatic pregnant woman with CML is unclear; a more liberal threshold of WBC 100-150 × 10^9/L has been suggested (Staley, 2018).

Leukocytapheresis has been performed in patients with APL with no improvement in outcome compared to patients receiving remission induction chemotherapy. One study found that leukocytapheresis in APL may contribute to early mortality (Vahdat, 1994). Central catheter placement and invasive procedures are generally avoided in APL patients during induction chemotherapy due to high risk of hemorrhage.

Rationale for therapeutic apheresis

Rapid reduction of the intravascular leukemic cellular burden by leukocytapheresis improves tissue perfusion with evidence of rapid reversal of pulmonary and CNS manifestations with leukocytapheresis.

Multiple retrospective studies of AML with hyperleukocytosis suggest that prophylactic leukocytapheresis can reduce the rate of early death (≤3 weeks into treatment); although there is no impact on later mortality and overall or long-term survival. Other studies have reported no benefit and raised concerns that leukocytapheresis might delay start of induction chemotherapy. A meta-analysis in patients with AML and initial WBC ≥100 × 10^9/L revealed that early mortality related to hyperleukocytosis in AML was not influenced by leukocytapheresis (Oberoi, 2014). A propensity score-matched study also showed leukocytapheresis did not have any positive influence on survival or other complications, such as TLS or DIC (Choi, 2018). Limitations to these studies include the retrospective, observational nature of the publications, and having moderate to high risk of confounding bias. Thus, leukocytapheresis may still have a therapeutic role in patients presenting with leukostasis. However, chemotherapy should not be postponed and is required to prevent rapid re-accumulation of circulating blasts.

Among children and adults with ALL, clinical symptoms of leukostasis develop in <10% at WBC <400 × 10^9/L. Therefore, prophylactic leukocytapheresis offers no advantage over aggressive induction chemotherapy and supportive care, including those with TLS. Pulmonary and CNS complications develop in >50% of children with WBC ≥400 × 10^9/L, suggesting that prophylactic leukocytapheresis might be beneficial in that setting.

Technical notes

A single leukocytapheresis can reduce the WBC by 30-60%. Erythrocyte sedimenting agents (hydroxyethyl starch, HES) are not required for AML or ALL. The use of low dose HES in leukocytapheresis is not associated with increased risk of renal failure. RBC priming may be employed for adults with severe anemia and/or low-weight children; however, RBC transfusion(s) prior to the procedure should be avoided, if possible, since it can increase viscosity and may worsen leukostasis. Platelet, cryoprecipitate and/or plasma transfusion, however, may be given if the patient has thrombocytopenia and/or coagulopathy prior to the procedure. Replacement fluid should be used to ensure at least a net fluid balance of ±15% of TBV, especially in unstable patients, pregnant patients, and pediatric patients. Calcium supplementation is advisable to prevent citrate toxicity. In patients <10 kg, manual whole blood exchange may be performed instead of using the automated cell separators.

Volume treated: 1.5-2 TBV	**Frequency:** Daily as needed

Replacement fluid: Crystalloid, albumin and/or plasma as needed

Duration and discontinuation/number of procedures

For AML patients with leukostasis, discontinue when the WBC count <50-100 × 10^9/L and symptoms resolved. For prophylaxis of AML patients, discontinue treatments when the WBC <100 × 10^9/L (closely monitor patients with myelomonocytic and monocytic subtypes). For ALL patients with leukostasis, discontinue when the WBC <400 × 10^9/L and symptoms resolved. For prophylaxis of ALL patients, discontinue treatment when WBC <400 × 10^9/L.

Keywords: hyperleukocytosis, leukostasis, leukapheresis, leukocytapheresis, acute leukemia

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HYPERTRIGLYCERIDEMIC PANCREATITIS

Incidence: 18/100,000/yr	**Indication**	**Procedure**	**Recommendation**	**Category**
	Severe HTG-AP	TPE/LA	Grade 1C	III
	Prevention of HTG-AP relapse	TPE/LA	Grade 2C	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
TPE/LA	0	3(66)	29(286)	NA

HTG-AP = hypertriglyceridemic acute pancreatitis

Description of the disease

After gallstones and alcohol, hypertriglyceridemia (HTG) is the third most common cause of acute pancreatitis (AP), accounting for 4-10% of cases. In pregnancy, relative frequency is up to 50%. HTG-AP is a complex disorder with an underlying mechanism that is influenced by genetic, metabolic, environmental and patient-specific factors. Triglyceride (TG) blood concentration is regulated by synthesis and metabolism of TG-rich lipoproteins, i.e., chylomicons reflecting enteral fat intake, and VLDL synthesized in the liver. Metabolism of TG is determined by the activity of endothelial lipoprotein-lipase (LPL) with several regulating factors (*apo CII, apoCIII, LMF1, GPIHBP1, apoAV,* and *ANGPTL 3/4*). Familial HTG, in particular the rare monogenic forms of chylomicronemia characterized by autosomal recessive genetic defects of LPL (prevalence 1:500,000) or its regulatory proteins, can lead to excessive HTG. Autoantibodies against LPL or its regulatory proteins can cause acquired chylomicronemia. Other primary causes of HTG include polygenic familial HTG, familial combined hyperlipidemia (FCHL), and familial dysbetalipoproteinemia. Secondary causes include diabetes mellitus (DM), nephrotic syndrome, hypothyroidism, pregnancy, inactivity, high-carbohydrate diets, excess alcohol intake, and different drugs. The atherogenic risk of HTG is increasingly recognized, but major morbidity caused by severe HTG is acute and relapsing pancreatitis (HTG-AP). HTG-AP appears to have a more severe course than AP due to other causes. In the literature HTG-AP is mostly discussed associated with severe HTG, i.e., TG levels >1,000 mg/dL and mortality from this complication may be up to 30%.

Current management/treatment

HTG-AP requires immediate supportive management and early detection of clinical deterioration that patient care can be escalated appropriately to reduce development of organ failure and limit sequelae. Treatment for HTG includes dietary restriction and lipid-lowering agent administration (fibrates or nicotinic acid derivatives). In addition, intravenous insulin and heparin have been proposed because they increase chylomicron breakdown and TG clearance by stimulating LPL synthesis and activity.

Rationale for therapeutic apheresis

The pathogenic model of HTG induced pancreatitis is disturbance of pancreatic microcirculation by very large TG-rich lipoproteins, with resulting ischemia, and subsequent hydrolytic release of free fatty acids that are toxic to the pancreatic endothelium and acinar cells. Extracorporeal elimination of large lipoproteins is hypothesized to stop further organ damage. Published evidence supporting the use of apheresis for HTG-AP is ambiguous. Correlation of pancreatitis severity and TG levels was not demonstrated using the APACHEII score (Gubensek, 2014), but became evident with the more organ specific revised Atlanta classification (Wang, 2016). TPE can significantly decrease TG levels, reduce inflammatory cytokines and potentially replace deficient LPL when plasma is used as replacement fluid. Reductions in TG levels of 49-97% have been reported following a single TPE procedure. Treatment goals are to reduce TG levels at least to mild-moderate levels. It is important to note that the TPE effect is transient; adequate lipid lowering treatment is essential to achieve a persistent effect.

In most studies, patients with secondary HTG were investigated, although the most benefit might be expected in chylomicronemia syndromes (Lennertz, 1999). Retrospective case control studies found no difference between standard therapy and TPE in patients with severe HTG-AP regarding mortality, systemic or local complications (Chen, 2004; Miyamoto, 2017). Information was not comprehensive to ascertain the comparability of the groups. Two small case control studies showed that use of TPE, or DFPP was associated with shortening of hospitalization, in particular if TG levels exceeded 5,000 mg/dl, or severe HTG-AP occurred during pregnancy (Huang, 2016). During pregnancy, TPE might play a more important role as treatment option because fibrates are contraindicated. Treatment has usually been implemented early in the course of HTG-AP though some authors have recommended its use only if there is no improvement with standard therapy. There was no difference in mortality between early (<36 hr after onset of pain) and late initiation of TPE (Gubensek, 2014). CS have reported on the use of maintenance TPE to maintain mild-moderately elevated TG levels to prevent further episodes of pancreatitis. For this indication selective LA procedures such as DFPP might be preferred to avoid the need of substituting human plasma products with their potential adverse effects.

Technical notes

Efficacy of membrane plasma separation for TPE can be impaired with chylomicronemia, so that use of centrifugal plasma separation is necessary. The use of LA techniques was successfully described (e.g., DFPP, dextran-sulfate adsorption from whole blood). However, these systems are optimized for the elimination of small to mid-sized apoB100-positive lipoproteins and efficacy can be reduced with chylomicronemia. According to its effect on LPL activity, heparin has been suggested as standard anticoagulant for these procedures. However, many reports have used ACD-A with similar TG reductions. Albumin was mostly used as the replacement fluid. Some have used plasma as it contains LPL and could enhance TG removal. No direct comparisons of replacement fluids have been reported.

Volume treated: 1-1.5 TPV **Frequency:** Therapeutic: daily for 1-3 days depending upon patient course and TG level; prophylactic use has not been investigated systematically, weekly to monthly treatment was reported to maintain TG at moderate levels.

Replacement fluid:
Albumin, plasma

Duration and discontinuation/number of procedures

For patients with AP, 1-3 TPE were enough to improve the patient's clinical condition and lower their TG levels with additional treatments if necessary. For patients treated prophylactically, chronic therapy for years has been reported.

Keywords: plasma exchange, hypertriglyceridemia, pancreatitis, chylomicronemia

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HYPERVISCOSITY IN HYPERGAMMAGLOBULINEMIA

Incidence: 5/1,000,000/yr	**Indication**	**Procedure**	**Recommendation**	**Category**
	Symptomatic	TPE	Grade 1B	I
	Prophylaxis for rituximab	TPE	Grade 1C	I
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Symptomatic	0	3(46)	21(279)	NA
Prophylaxis for rituximab	0	0	3(45)	3(3)

Description of the disease

Whole blood viscosity varies as a function of hematocrit, RBC aggregation, plasma proteins, and interactions between the blood and the blood vessel wall. As blood viscosity rises, a nonlinear increase in shear stress in small blood vessels, particularly at low initial shear rates, produces damage to fragile venular endothelium such as that of the eye and other mucosal surfaces. Hyperviscosity syndrome (HVS) refers to the clinical sequelae caused by the altered physiology related to plasma hyperviscous states, most typically seen in Waldenström's macroglobulinemia (WM) associated with monoclonal IgM or, less frequently, with multiple myeloma (MM) associated with monoclonal IgA or IgG3. Signs and symptoms of HVS include headache, dizziness, nystagmus, hearing loss, visual impairment (retinal hemorrhage/detachment), somnolence, coma, and seizures. Other manifestations include congestive heart failure (related to plasma volume overexpansion), respiratory compromise, coagulation abnormalities, anemia, fatigue, peripheral polyneuropathy, and anorexia. When the IgM protein associated with WM exceeds a concentration of 4 g/dL, the relative plasma viscosity can exceed 4 centipoise (cp; relative to water: normal range, 1.4-1.8 cp) and HVS can occur. Serum viscosity measurement does not consistently correlate with clinical symptoms among individual patients, however, the viscosity level at which the syndrome appears is generally reproducible within the same patient (symptomatic threshold). Most patients will be symptomatic at levels of 6-7 cp. HVS occurs in MM with 6-7 g/dL of monoclonal IgA or 4 g/dL of monoclonal IgG3 in the plasma.

Current management/treatment

The current standard of care for HVS is removal of the paraprotein by TPE. Early diagnosis, which can usually be made from the funduscopic exam, is crucial to prevent further progression. TPE should be carried out as soon as the diagnosis is made. TPE does not affect the underlying disease process, thus systemic chemotherapy or immunotherapy should be initiated soon after TPE as serum IgM levels will return to baseline in 4 -5 weeks. Patients with WM are usually managed using a risk-adapted approach. Patients with constitutional symptoms, hematological compromise, and bulky disease should be considered for chemotherapy +/- immunotherapy. A combination of bendamustine and rituximab has been recommended as first line therapy for bulky disease, while dexamethasone-rituximab-cyclophosphamide has been suggested as an alternative, especially in the setting of non-bulky disease. Other regimens include proteasome inhibitors (bortezomib and carfilzomib), nucleoside analogs (fludarabine and cladribine), and ibrutinib. For patients with preserved hematological function and IgM monoclonal gammopathy of undetermined significance (MGUS) (<10% lymphoplasmacytic marrow infiltration) watchful waiting is most appropriate. Pregnant patients unable to receive systemic therapy may be candidates for TPE.

Rationale for therapeutic apheresis

TPE has been successfully used since the late 1950s and has been shown to promptly reverse retinopathy and other clinical manifestations of HVS. IgM is 80% intravascular and serum viscosity rises steeply with increasing IgM levels. Thus, a relatively small reduction in IgM concentration has a significant effect on lowering serum viscosity. TPE reduces viscosity 20-30% per treatment.

A transient increase in IgM level after rituximab therapy (flares), has been reported in 30-70% of patients within 4 weeks of treatment initiation. TPE should be considered before giving rituximab if serum viscosity >3.5 cp or IgM level >4 g/dL. Acquired von Willebrand disease has been reported in WM; low von Willebrand factor levels are associated with higher concentration of IgM and hyperviscosity. Whether patients with IgM proteins having autoantibody activity and consequent immune-mediated organ damage should receive more aggressive TPE is unknown.

Technical notes

Conventional calculations of plasma volume based on weight and hematocrit are inaccurate in M-protein disorders because of plasma volume expansion. Cascade filtration and membrane filtration techniques have been described and may have similar efficacy in removing M-protein.

Volume treated: 1-1.5 TPV	**Frequency:** Daily or every other day
Replacement fluid: Albumin, plasma (if daily)	

Duration and discontinuation/number of procedures

Daily or every other day TPE until acute symptoms abate (generally 1-3 procedures). Clinical monitoring, viscosity as well as IgM levels are recommended during treatment to determine if subsequent TPE procedures are necessary. The reduction in IgM may be less than the theoretical reduction of an ideal solute (Miyamoto, 2018). Retinal changes in otherwise asymptomatic patients with WM respond dramatically to a single TPE with marked or complete reversal of the abnormal exam findings. When patients are maintained at a level under their symptomatic threshold, clinical manifestations of the syndrome usually are prevented. A maintenance schedule of TPE every 1-4 weeks based on clinical symptoms or retinal changes may be employed to maintain clinical stability while initiating chemotherapy +/-immunotherapy. Prophylactic TPE is performed to lower IgM to <4 g/dL prior to rituximab therapy.

Keywords: Hyperviscosity syndrome, monoclonal gammopathy, Waldenström's macroglobulinemia, multiple myeloma, M-protein, plasma exchange

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IgA NEPHROPATHY (BERGER'S DISEASE)

Incidence: 4/100,000 with 5-10% developing RPGN	**Indication**	**Procedure**	**Recommendation**	**Category**
	Crescentic	TPE	Grade 2B	III
	Chronic progressive	TPE	Grade 2C	III
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	2(24)	7(64)	8(10)

RPGN = rapidly progressive glomerulonephritis

Description of the disease

Immunoglobulin A nephropathy is the most common form of glomerulonephritis in the developed world, particularly in Asians and Caucasians. It is frequently asymptomatic with a benign course (no severe kidney damage) but there are reports of slow progression to end stage renal disease (ESRD) over 20-25 years in up to 50% of patients (chronic progressive) and, less commonly, the aggressive crescentic form can occur. Histologically, glomerular deposits of IgA characterize IgA nephropathy. Roughly >10% of patients can present as rapidly progressive crescentic glomerulonephritis. When there are symptoms, the classic presentation for the disease is gross hematuria occurring shortly after an upper respiratory infection (synpharyngitic) or, when asymptomatic, discovery of microscopic hematuria with or without proteinuria. Factors associated with disease progression are hypertension, persistent proteinuria >1000 mg/day, and elevations in serum creatinine. The crescentic form (CreIgAN) is characterized by acute kidney injury with gross hematuria. While the pathophysiology has not been definitively characterized, current theory focuses on dysregulation of mucosal immune response: 1) mucosal B cells migrate to the bone marrow where they produce galactose-deficient IgA1, 2) IgG autoantibodies are generated toward this Gd-IgA1, 3) GD-IgA1-IgG complexes with soluble CD89 (sCD89) are deposited in the mesangium of the glomerulus, 4) elevated levels of complement products (C3a, C5a, C5b-9) and mesangial IgA receptors are activated, 5) mesangial cell damage activates additional pathways, and 6) glomerulosclerosis and interstitial fibrosis develops.

Current management/treatment

Therapy consists of blood pressure control, control of proteinuria with ACE inhibitors or angiotensin receptor blockers, control of hypercholesterolemia using HMG-CoA inhibitors, omega-3 fatty acids, and glucocorticoids with or without other immunosuppressant agents such as cyclophosphamide or azathioprine. The NEFIGAN double blind randomized study showed that the targeted-release of budesonide to the gut mucosa could influence the course of IgAN in 149 patients positively (Fellström, 2017). Eculizumab is also used in cases with the clinical and laboratory signs of atypical HUS.

Rationale for therapeutic apheresis

The rationale for TPE in IgA nephropathy is for the removal of circulating plasma Gd-IgA-IgG complex levels and complement products (C3a, C5, and soluble C5b-9). Early positive experiences of the use of TPE in treating some forms of RPGN resulted in the application of TPE to cases presenting with crescentic form. In addition, early studies demonstrated that TPE could reduce the circulating IgA and IgA immune complexes levels. Most published experience has looked solely at the treatment of the CreIgAN form of the disease and not the chronic progressive disease.

CRs and CS from previous decades have addressed the treatment of the rapidly progressive form. Most of these patients were treated with TPE and concurrent corticosteroids and/or immunosuppressants with reported improvement in kidney function and decrease in serum IgA. Numerous authors have found that improvement only occurred in the presence of cellular crescents, and not in sclerotic, scarred glomeruli. Two early reports involving 32 patients used only TPE, without other therapy, and saw improvement in kidney function in 31 of these patients. A CT examined three patients treated with corticosteroids and immunosuppressants and six who also received TPE. Two of the 3 patients who received only corticosteroids and immunosuppressants became dialysis dependent while the 6 receiving TPE demonstrated resolution of kidney failure during therapy. However, after discontinuation of TPE, disease progressed in all 6, with 3 being dialysis dependent at 3 years following TPE and the remaining having mild to moderate chronic kidney disease (Roccatello, 2000). This trial is representative of the experiences reported in CS and CRs.

One controlled study including 12 patients compared with 12 historical controls indicated that adding TPE to immunosuppressive therapy (glucocorticoids and cyclophosphamide) could increase renal recovery rates in severe CreIgAN and could significantly reduce plasma IgA-IgG complex levels including complement product levels (Xie, 2016). The question of whether TPE can avoid ESRD is still open.

Technical notes

Volume treated: 1-1.5 TPV	**Frequency:** 6-9 over 21 days followed by 3-6 over 6 weeks.
Replacement fluid: Albumin or plasma	

Duration and discontinuation/number of procedures

A fixed course of therapy has been used to treat patients presenting with CreIgAN. Creatinine is monitored to determine response. In chronic progressive disease, chronic therapy with weekly TPE has been reported.

Keywords: plasma exchange, plasmapheresis, IgA nephropathy, immune complex rapidly progressive glomerulonephritis, rapidly progressive glomerulonephritis

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IMMUNE THROMBOCYTOPENIA (ITP)

Incidence: 20-40/1,000,000/yr (adults); 40-50/1,000,000/yr (children)	**Indication**	**Procedure**	**Recommendation**	**Category**
	Refractory	TPE/IA	Grade 2C	III
# reported patients: 100-300	**RCT**	**CT**	**CS**	**CR**
TPE	0	0	4(30)	3(3)
IA	0	0	6(136)	NA

Description of the disease

Immune thrombocytopenia (ITP) is the most common autoimmune hematologic disorder. It is an acquired thrombocytopenia where autoantibodies or immune complexes are bound to platelet surface antigens, primarily GPIIb/IIIa and/or GPIb/IX, causing accelerated platelet destruction. Primary ITP, which is a diagnosis of exclusion, is characterized by isolated thrombocytopenia without known initiating or underlying cause. By a consensus conference, ITP was classified into newly diagnosed ITP (0 to 3 months), persistent ITP (3 to 12 months), chronic ITP (lasting more than 12 months), and refractory ITP (refractory to standard treatment). Childhood ITP is generally acute, benign, self-limited, and typically presents with abrupt onset of petechiae, bruising and/or epistaxis following viral infection. Peak age is 2-5 years old with both sexes affected equally. In the majority of childhood ITP, no treatment is required; however, 20% of patients will not spontaneously recover and will continue to be thrombocytopenic. Adult ITP, which predominantly affects women aged 18-40 years, usually has an insidious onset and 40-50% become chronically thrombocytopenic. Up to 20% of adult ITP is secondary to an underlying primary disorder or stimulus, such as systemic lupus erythematosus, lymphoproliferative disorders, drug ingestion, primary immunodeficiency or infections, especially hepatitis and HIV. ITP in adults is more serious than in children, because the risk of fatal bleeding increases with age. At platelet counts $<30 \times 10^9$/L, in patients younger than 40, 40-60, and >60 years old, this risk is 0.4%, 1%, and 13% per patient year, respectively.

Current management/treatment

Treatment is generally not indicated when the platelet count is $>20\text{-}30 \times 10^9$/L unless bleeding (including mucosal bleeding) occurs. First-line therapies are oral corticosteroids (1-2 mg of prednisone/kg/day), IVIG at 1 g/kg/day for 1-2 days, and IV anti-RhD (50-75 μg/kg). In adults, corticosteroids remain the standard primary therapy. For most children, a “watch and wait” approach is often taken after other diagnoses are excluded. For those children requiring treatment, IVIG or a single dose of anti-RhD in RhD positive patients may be substituted for prednisone for rapid response. If thrombocytopenia persists or recurs, splenectomy is often preferred as second-line therapy, but more recent data suggests less than 25% of patients with ITP undergo splenectomy; rituximab or thrombopoeitin receptor agonists are increasingly being used before patients are referred for splenectomy. In children, splenectomy is deferred for one year to avoid overwhelming postsplenectomy infection and to allow for spontaneous remission. Other salvage therapies such as danazol, vinca alkaloids, cyclophosphamide, azathioprine and cyclosporine, may be considered based on bleeding, clinical risks and patient-specific considerations.

Rationale for therapeutic apheresis

Anecdotal CRs and small CS of patients with chronic ITP have described a potential benefit for TPE when combined with other salvage therapies, such as prednisone, splenectomy, IVIG, and cytotoxic agents. However, TPE has been shown to be ineffective in other studies. In one report, no improvement was observed, among five patients who underwent TPE for refractory ITP, after splenectomy (Cotter, 1983). In another, the 6-month response rate and rate of splenectomy were no different among 12 patients who received TPE plus prednisone compared to seven patients treated with prednisone alone (Buskard, 1998). IA may be considered in patients with refractory ITP, with life-threatening bleeding or in whom splenectomy is contraindicated. Columns have a high affinity for IgG and IgG-containing circulating immune complexes that can be selectively removed from the patient’s plasma. Studies of IA have demonstrated a range of outcomes from no improvement to complete remission for longer than 6 years. In one of the larger studies, 72 patients were given six IA treatments over 2-3 weeks with 29 (40%) of the patients continued on low dose corticosteroids during IA therapy. Approximately 25% of the patients had a good response (platelet count $>100 \times 10^9$/L) while 21% had a fair response (platelet count $50\text{-}100 \times 10^9$/L). Over half the patients (54%) had a poor response (Snyder, 1992). The staphylococcal protein A column was removed from the market in 2006 and more recent studies with IA used other commercially available systems. Most recent studies used TPE and IA in combination with other treatment modalities (glucocorticoids, IVIG) or as preparative treatment to achieve a splenectomy in severely and refractory thrombocytopenic patients.

In children, extra care must be given to maintain isovolemia because of the large extracorporeal volume involved with the IA procedure.

Technical notes

Volume treated: IA: 2-4 TPV; TPE: 1 TPV	**Frequency:** IA: Once a week or every 2-3 days; TPE: Daily or every other day
Replacement fluid: IA: NA; TPE: Plasma or albumin	

Duration and discontinuation/number of procedures

There are no clear guidelines concerning treatment schedule and duration of treatment. The series of procedures is generally discontinued when either the patient shows improvement in platelet count $>50 \times 10^9$/L or no improvement after approximately 6 treatments.

Keywords: immune thrombocytopenia, plasma exchange, immunoadsorption

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INFLAMMATORY BOWEL DISEASE

Incidence: UC: 35--100/100,000; CD: 27-48/100,000		Indication	Procedure	Recommendation	Category
		UC/CD	Adsorptive cytapheresis	Grade 1B	III
		CD	ECP	Grade 2C	III
# reported patients: >300		**RCT**	**CT**	**CS**	**CR**
UC	Adsorptive cytapheresis	12(724)	9(92)	NA	NA
CD	Adsorptive cytaphereis	2(258)	1(104)	NA	NA
CD	ECP	0	0	3(69)	2(3)

UC = ulcerative colitis; CD = Crohn's disease

Description of the disease

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory diseases of the gastrointestinal tract and are collectively known as inflammatory bowel disease (IBD). The phenotype of these disorders is variable, affecting predominately individuals in the third decade of life. The incidence of IBD is highest in North America, Europe and Scandinavia; however, it has a worldwide distribution. Environmental, gut microbiota and genetic factors may lead to leukocyte recruitment to the gut mucosa. The cells, and accompanying cytokines and proinflammatory mediators, cause progressive tissue damage and lead to the debilitating clinical manifestations of IBD.

Current management/treatment

First-line therapies for IBD include anti-inflammatory agents, steroids and immunosuppressive medications. Both corticosteroids and 5-aminosalicylic acids (5-ASAs) are effective in achieving remission. In addition, 5-ASAs and immunosuppressant drugs reduce the risk of subsequent relapse of activity in quiescent disease. Unfortunately, complications from chronic steroid administration include steroid resistance, dependency and the sequelae of long-term steroid use. For those with refractory disease, thiopurines, such as azathioprine and 6-mercaptopurine, are used. In CD specifically, infliximab, a monoclonal antibody to anti-tumor necrosis factor, may induce remission and has been FDA approved for this purpose. Surgical intervention may be necessary in some patients.

Rationale for therapeutic apheresis

Selective apheresis is a potentially useful adjunct for the management of IBD with the goal of removing the activated leukocytes or moderating their proinflamatory nature towards an immune modulatory phenotype. A meta-analysis synthesized the findings of 9 RCTs examining granulocytapheresis using the Adacolumn to treat UC (Yoshino, 2014). This treatment was effective for achieving a clinical response in patients with active UC when compared to corticosteroids. Intensive therapy (>2 sessions per week) resulted in a higher remission rate when compared to patients treated weekly. However, one RCT showed no difference in the remission rate when adsorptive cytapheresis was compared to sham treatment (Sands, 2008). A post-hoc analysis of this study demonstrated that the treated subset of patients with microscopic erosions/ulcerations had a significantly higher remission rate when compared to the sham group (Kruis, 2015). Factors that may impact response to therapy in UC include disease activity level, duration and response to corticosteroids. Conventional therapy in US includes immunosuppression with TNFα blockade whereas conventional therapy in Japan consists of steroids and aminosalicylates alone. It is possible that this accounts for positive outcomes for adsorptive cytapheresis found in Asian, but not North American studies.

Evidence supporting the use of adsorptive cytapheresis to treat CD is more limited. Although a few uncontrolled studies have demonstrated efficacy in the treatment of active CD, a large RCT did not demonstrate any difference in remission rates when compared to sham treatment in patients with moderate to severe CD (Sands, 2013). Two uncontrolled CS have been published suggesting that ECP can promote remission for a proportion of patients with steroid and/or immunosuppressant intolerant CD (Abreu, 2009; Reinisch, 2013).

Technical notes

Two types of selective apheresis devices are the Cellsorba (Asahi Medical, Tokyo, Japan) which is a column containing cylindrical non-woven polyester fibers and, the Adacolumn (JIMRO, Japan) which contains cellulose acetate beads. Both require anticoagulation (heparin/ACD-A and heparin alone, respectively) to remove granulocytes and monocytes from venous whole blood by filtration/adhesion. For Cellsorba, venous whole blood is processed at 50 mL/min through the column for 60 minutes. Some platelets and lymphocytes are also removed by this column. For Adacolumn, venous whole blood is processed at 30 mL/min for 60 minutes. The Adacolumn is relatively selective for removing activated granulocytes and monocytes. Patients taking ACE inhibitors may experience low blood pressure if undergoing treatment with Adacolumn. Cellsorba and Adacolumn are currently available in Japan. The two columns have been compared in a prospective clinical trial that demonstrated equivalent response in patients with moderate-to-severe active UC (Sakata, 2008).

Volume treated: Adacolumn: 1800 mL; Cellsorba: 3000 mL	**Frequency:** Once per week, more intensive therapy may include daily to two times per week
Replacement fluid: NA	

Duration and discontinuation/number of procedures

The typical length of treatment is 5-10 weeks for Adacolumn and 5 weeks for Cellsorba.

Keywords: Adacolumn, Cellsorba, granulocyte and monocyte adsorption apheresis, leukocytapheresis, selective apheresis, adoptive cytapheresis, granulocyte monocyte adsorptive apheresis, leukocytapheresis, Crohn's disease, ulcerative colitis, inflammatory bowel disease

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LAMBERT-EATON MYASTHENIC SYNDROME

Incidence: <1/1,000,000		**Procedure**	**Recommendation**	**Category**
		TPE	Grade 2C	II
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	7(43)	5(6)

Description of the disease

The Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune disorder affecting the pre-synaptic neuromuscular junction (NMJ). Its classical clinical triad includes muscle weakness (most prominent in proximal muscles of the lower extremities), hyporeflexia and autonomic dysfunction (e.g., dry mouth, constipation and male impotence). In contrast to myasthenia gravis (MG), brain stem symptoms such as diplopia and dysarthria are uncommon. Approximately 60% of cases occur as a paraneoplastic disorder, most commonly associated with small cell lung cancer (SCLC). LEMS is estimated to occur in 3-6% of patients with SCLC. Other cancers such as lymphoma, malignant thymoma and Merkel cell carcinoma have been reported in association with LEMS. Rapid onset and progression of symptoms over weeks or months should heighten suspicion of underlying malignancy. While SCLC-LEMS typically presents at a median age of 60 years with a male predominance, non-tumor LEMS has a median age of 35 years and is often associated with other autoimmune diseases. LEMS is very rare in children.

The diagnosis of LEMS is confirmed by electrophysiological studies. Autoantibodies directed at the P/Q type voltage-gated calcium channel (VGCC) of the NMJ are found in 85-90% of patients (Titulaer, 2011). The antibodies are believed to cause insufficient release of acetylcholine quanta by action potentials arriving at motor nerve terminals. Unlike MG, which is characterized by antibodies to the postsynaptic acetylcholine receptor, VGCC antibodies target the pre-synaptic structure. Antibody levels do not correlate with severity but may decrease as the disease improves in response to immunosuppressive therapy. SRY-Box 1 (SOX1) antibodies are an additional characteristic of 65% of patients with paraneoplastic LEMS.

Current management/treatment

Apart from a search for, and treatment of, underlying malignancy, management of LEMS is directed toward support of acetylcholine-mediated neurotransmission to improve neurological function and immunosuppression to control production of the autoantibodies. Aminopyridines [3,4-DAP (3,4-Diaminopyridine) or 3,4-DAP phosphate] are the first choice for symptomatic control in LEMS. These medications block fast voltage-gated potassium channels, prolonging presynaptic depolarization and thus the action potential, resulting in increased calcium entry into presynaptic neurons and increased release of acetylcholine. Cholinesterase inhibitors such as pyridostigmine tend to be less effective given alone than they are in MG but can also be used.

If symptomatic therapy is unsatisfactory immunosuppression is indicated. Recommendations for immunosuppressive therapies are very similar to those for MG and include oral corticosteroids, azathioprine, cyclosporine, IVIG, and TPE. Studies have reported significant improvement following the combination treatment of corticosteroids and azathioprine. IVIG has been shown effective in LEMS in a randomized, double-blind, placebo-controlled crossover trial involving 9 patients. IVIG may be useful in repeated monthly infusion of 2 g/kg given over 2-5 days over upward of 2 years. In addition, rituximab has also shown to be effective in some cases. In general, it should be noted that LEMS in most cases requires long-term treatment.

Rationale for therapeutic apheresis

The identification of LEMS as an autoantibody-mediated syndrome has led to several attempts to use TPE in its treatment. While no CTs exist on the use of TPE in LEMS, CS have suggested a benefit. In one CS, 8 out 9 patients had increase in electromyographic muscle action potential ($p < 0.01$) while receiving TPE and immunosuppression (Newsom-Davis, 1984). TPE produces relatively rapid, albeit temporary (~6 weeks), improvement in most LEMS patients. In addition, patients tended to worsen after completion of TPE if additional immunosuppressive therapy was not employed. TPE may be a useful adjunct to management of patients with LEMS whose neurological deficit is severe or rapidly developing, in the case of patients who are too uncomfortable to wait for immunosuppressive or aminopyridine drugs to take effect, or who cannot tolerate treatment with IVIG. IA might be an alternative treatment option; however, data are even more limited for IA than for TPE (Sauter, 2010).

Technical notes

The reported TPE regimens vary from 5-15 TPE over 5-19 days to 8-10 TPE carried out at 5-7-day intervals. Regimes must be adjusted according to symptom response. Most reports indicate an exchange volume of 1-1.5 plasma volumes. Of note, improvement may not be seen for 2 weeks or more after initiation of TPE. This may be due to the slower turnover of the presynaptic VGCC compared to the postsynaptic acetylcholine receptor.

Volume treated: 1-1.5 TPV	**Frequency:** Daily or every other day
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

Treatment should continue until a clear clinical and EMG response is obtained or at least until a 2-3-week course of TPE has been completed. Repeated courses may be applied in case of neurological relapse, but the effect can be expected to last only up to 6 weeks in the absence of immunosuppressive therapy.

Keywords: Lambert-Eaton Myasthenic Syndrome, plasma exchange

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LIPOPROTEIN(a) HYPERLIPOPROTEINEMIA

Prevalence: ≈20% Lp(a) levels >50 mg/dl	**Indication**	**Procedure**	**Recommendation**	**Category**
	Progressive ASCVD	LA	Grade 1B	II
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	3(61)	3(283)	NA	NA

ASCVD = atherosclerotic cardiovascular disease, Lp(a) = Lipoprotein(a)

Description of the disease

After the first description of Lipoprotein(a) (Lp(a)) in 1963, the Copenhagen City Heart Study, in 2008, was seminal for the renaissance of recognizing Lp(a) as independent, and causal risk factor of atherosclerotic cardiovascular disease (ASCVD) in the general population (i.e., coronary artery disease, calcific aortic valve disease, peripheral arterial disease, and stroke). Subsequent pathophysiological research, epidemiologic studies, and Mendelian randomization studies confirmed this role.

Lp(a) is composed of an LDL-like particle to which a single copy of apolipoprotein(a) (apo(a), encoded by the *LPA*-gene) is covalently attached. The physiological function of Lp(a) is still unknown. Apo(a) is composed of an inactive protease domain, and plasminogen-like kringle (K) domains. Ten different KIV domains have evolved in the *LPA* gene, which show an extensive repeat copy number variation resulting in >40 Lp(a) isoforms of different size. In approximately 80%, *LPA* is heterozygous with more abundant expression of the smaller isoform. The number of circulating Lp(a)-particles is mainly genetically determined with significant racial differences of Lp(a) concentration and isoform distribution. Lp(a) concentration and isoform size are inversely correlated. Patients with familial hypercholesterolemia typically have higher mean Lp(a) concentrations. Kidney disease can also lead to increased Lp(a) levels.

Lp(a) exerts all atherogenic effects of an LDL-particle. Bound oxidized phospholipids, accumulation in atherosclerotic plaques, and antifibrinolytic effects are additional features. Cardiovascular risk exhibits a nearly linear association with increasing Lp(a) concentration. Due to the Lp(a) isoform polymorphism, mass calibrated measurements (i.e., in mg/dL) can't be converted in molar units (i.e., nmol/L) by a simple conversion factor.

Current management/treatment

The Consensus Panel of the European Atherosclerosis Society published a Lp(a) concentration below the 80th percentile (<50 mg/dL) as desirable, not claiming that this is a treatment target. Diet or lifestyle have no influence on Lp(a) concentration. There are currently no drugs approved to treat Lp(a)-hyperlipoproteinemia (Lp(a)-HLP). Statins can induce an increase of Lp(a) by approximately 10%. Other existing lipid lowering drugs reduce Lp(a) concentration, however, the clinical relevance of this effect is unknown: nicotinic acid by approximately 39%, the apoB-antisense-oligonucleotide mipomersen by approximately 25%, and PCSK9-antibodies alirocumab and evolocumab up to 30%, but only with low Lp(a) levels. Antisense oligonucleotides inhibiting apo(a) synthesis and Lp(a) secretion in the liver have shown promising results in phase 2 clinical trials with up to 80% reduction (Viney, 2016).

Rationale for therapeutic apheresis

All currently available lipoprotein apheresis (LA) systems can decrease Lp(a) in the range of >60-80% immediately after a single session. A few RCTs and CTs have investigated the use of LA in patients with Lp(a)-HLP with a and demonstrated relief of refractory angina, improved myocardial perfusion, regression of coronary stenosis, or increased patency of vein grafts after coronary artery bypass graft. Small patient numbers, limited periods of LA treatment, or in part including patients without substantial Lp(a)-HLP limit the significance of results. Several studies used the design of comparing incidence rates of cardiovascular events, before and after commencing chronic LA treatment of patients with Lp(a)-HLP and severe ASCVD, with observation periods of 2-5 years. Lack of a control group is a limitation of these studies, however, results consistently demonstrated that LA was effective to prevent cardiovascular events, thus reverting a progressive course of ASCVD to a stable course.

Due to the huge prevalence of elevated Lp(a) concentrations in the general population, additional criteria are mandatory for the indication of Lp(a) lowering treatment, in particular LA. The German reimbursement guideline existing since 2008 introduced the Lp(a) threshold >60 mg/dL (equivalent to >120 nmol/L) associated with the clinical condition of progressive ASCVD in coronary, peripheral, or cerebrovascular territories (Leebmann, 2013). Positive family history, or premature manifestation of ASCVD are important aspects when considering Lp(a) associated cardiovascular risk. Attributing Lp(a) as the major risk factor for the progressive course of ASCVD in an individual patient requires, that all other cardiovascular risk factors should be under optimized treatment. Targeted treatment of concomitant hypercholesterolemia must be an initial step. For the assessment of the distance to the target LDL-cholesterol (LDL-C), measured LDL-C should be corrected for the Lp(a)-cholesterol contribution: $LDL\text{-}C_{corrected}$ [mg/dL] = $LDL\text{-}C_{measured}$ [mg/dL] - 30% of Lp(a) [mg/dL]. Detailed selection criteria, in particular how to define progression clinically or with imaging techniques, or agreement on thresholds of achieved LDL-C are the subject of current research. Implementation of these criteria into routine care to approve the indication for LA due to Lp(a)-HLP differs according to national reimbursement regulations and must be further refined with growing experience.

Technical notes

Angiotensin converting enzyme (ACE) inhibitors are contraindicated in patients undergoing adsorption-based LA due to increased bradykinin generation, leading to profound hypotension.

Volume treated: Plasma or whole blood volumes vary according to recommendations of device manufacturers.	**Frequency:** Once every 1-2 weeks
Replacement fluid: NA	

Duration and discontinuation/number of procedures

Treatment is continued indefinitely. Lp(a) target levels to guide LA frequency, e.g., time averaged or post-LA concentration have not been defined. A single session should have a >60% reduction of pre-LA Lp(a) concentration.

Keywords: LDL apheresis, lipoprotein apheresis, lipoprotein(a), Lp(a), apolipoprotein(a), coronary heart disease, cardiovascular disease, hyperlipoproteinemia

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MALARIA

Incidence: 216 million cases worldwide in 2016; 1700 cases in US	Indication	Procedure	Recommendation	Category
	Severe	RBC Exchange	Grade 2B	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
RBC exchange	0	1(415)*	NA	NA
Manual exchange transfusion	0	8(279)	9(128)	NA

*Automated and manual RBC exchange

Description of the disease

Malaria is vector-borne protozoal infection caused by *Plasmodium vivax, P. ovale, P. malariae* or *P. falciparum.* Although mortality has declined worldwide, malaria still causes >400,000 deaths annually. The highest mortality occurs with *P. falciparum* in Africa in pregnant women, nonimmune travelers, those with HIV/AIDS and children <5 years. The intraerythrocytic stage of the *Plasmodia* life cycle is responsible for the pathological disease manifestations. Parasitemia leads to RBC rigidity and aggregation, microvascular obstruction, hemolysis and activation of inflammatory cells and cytokines. *P. falciparum* is responsible for most severe malaria cases, characterized by high-grade (>5%) parasitemia with or without single organ or multisystem dysfunction (impaired consciousness, seizures, pulmonary edema, acute respiratory distress syndrome, shock, disseminated intravascular coagulation, acute kidney injury, hemoglobinuria, jaundice, severe anemia (Hgb <5 g/dL), acidosis, and hypoglycemia). Mortality rate with severe *P. falciparum* malaria is 5-20%. Poor prognostic features include older age, shock, acute kidney injury, acidosis, decreased level of consciousness, preexisting chronic disease, progressive end-organ dysfunction, anemia, and hyperparasitemia >10%. Because severe complications can develop in up to 10% of nonimmune travelers with *P. falciparum*, symptomatic patients with a positive travel history should be promptly evaluated and treated.

Current management/treatment

Malaria treatment is based on clinical status of the patient, *Plasmodium sp.* involved, and drug-resistance pattern predicted by geographic region of acquisition. Management of imported, uncomplicated malaria in the US is outlined in guideline documents available from the Centers for Disease Control and Prevention (CDC). Severe malaria should be treated promptly with intravenous quinidine gluconate and transition to oral quinine-combinations when stable. Intravenous artesunate is available through the CDC for intolerance or contraindications to quinidine or for drug-resistance manifested by parasitemia >10% at 48 hrs of treatment. *P. falciparum* with severe anemia, hypoxemia, hyperparasitemia, neurologic manifestations or metabolic derangements, particularly in children, asplenic or immunocompromised individuals, requires aggressive parenteral antimalarials. Intensive care support is also often necessary.

Rationale for therapeutic apheresis

RBC exchange or manual exchange transfusion (ET; with whole blood or RBC replacement) in severely ill patients with hyperparasitemia (>10%) appears to improve blood rheological properties, capillary perfusion and microcirculatory flow by removing infected RBC thus reducing parasite load and modulating cytoadherence. Whole blood ET may also reduce pathogenic humoral mediators, such as parasite and host toxins, hemolytic metabolites, and cytokines, and replenish deficient proteins (ADAMTS13, clotting factors). CRs have described rapid clinical improvement and improved parasite clearance times with severe *P. falciparum* when RBC exchange or manual ET is used in conjunction with intravenous quinidine therapy. However, parasite clearance time with artesunate alone is rapid and similar to that achieved by automated RBC exchange. The role for and potential benefit of automated or manual ET in severe malaria is controversial and based on observational retrospective clinical data. Meta-analysis of 279 patients from 8 CTs found no survival benefit of manual ET compared to antimalarials and aggressive supportive care (Riddle 2002). Notably, there were major differences in ET methodologies, severity of illness in transfusion versus non-transfusion groups and other confounding variables that question accuracy of these comparisons and the analyses. The CDC reported on 101 patients with severe malaria who received ET compared to 314 who did not and demonstrated no difference in mortality and thus no longer recommend ET use. Limitations to this underpowered study were lack of critical data on ET specifics (manual versus automatic, full or partial; whole blood versus RBC), lack of parasitemia level in many patients, lack of survival data in ET patients, exclusion of ET survival cases, and imperfect matching of cases and controls (Tan 2013). Based on this study, the CDC no longer recommends exchange transfusion for the treatment of severe malaria. The 2016 UK treatment guidelines for severe malaria no longer recommend exchange transfusion, citing the rapid action of artesunate in reducing parasite burden. WHO guidelines make no recommendation regarding ET use, citing lack of consensus on indications, benefits, dangers and practical technical details. Rare CRs have described using adjunctive TPE with automated RBC exchange; however, lack of published experience precludes assessment of this in patients with severe malaria.

Technical notes

Automated apheresis instruments calculate the amount of RBCs required to achieve the desired post-procedure hematocrit, fraction of RBCs remaining and, by inference, the estimated final parasite load. One 2-volume RBC exchange can reduce the fraction of remaining patient RBCs to roughly 10-15% of the original. The additional risks in developing countries may include transfusion-transmitted infections.

Volume treated: 1-2 total RBC volumes	**Frequency:** 1-2 treatments
Replacement fluid: RBCs (consider leukoreduced)	

Duration and discontinuation/number of procedure

Treatment is typically discontinued after achieving significant clinical improvement and/or <1% residual parasitemia.

Keywords: malaria, RBC exchange, exchange transfusion, falciparum

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MULTIPLE SCLEROSIS

Incidence: 8-9/100,000/yr (North America/Western, Northern Europe)		**Indication**	**Procedure**	**Recommendation**	**Category**
		Acute attack/relapse	TPE	Grade 1A	II
			IA	Grade 1B	II
		Chronic PPMS/SPMS*	TPE	Grade 2B	III
			IA	Grade 2B	III
# reported patients: >300		**RCT**	**CT**	**CS**	**CR**
Acute attack/relapse	TPE	2(138)	0	20(419)	NA
	IA	0	0	9(316)	NA
Chronic PPMS/SPMS*	TPE	4(300)	2(50)	NA	NA
	IA	0	0	2(27)	0

*PPMS/SPMS = primary or secondary progressive MS

Description of the disease

Multiple sclerosis (MS) is the most prevalent chronic inflammatory demyelinating disease of the central nervous system (CNS), affecting at least 400,000 patients in the US with 2:1 female preference. It is currently incurable. Typical symptoms at presentation include, but are not limited to, monocular visual loss due to optic neuritis, limb weakness or sensory loss due to transverse myelitis, double vision due to brain-stem dysfunction, or ataxia due to a cerebellar lesion. Acute demyelinating optic neuritis is the presenting feature in 15-20% of patients, and it occurs in 50% at some time. The clinical course can be classified as clinically isolated syndrome (CIS), relapsing-remitting (RRMS), and primary or secondary progressive (PPMS, SPMS). After 10-20 years, a (secondary) progressive course develops in many patients, leading to neurologic disability, but 15% of all have a progressive course from the onset of the disease. MS lesions can appear throughout the CNS and are recognized in the white matter as focal areas of demyelination, inflammation, and glial reaction. Humoral as well as cell mediated autoimmunity, along with genetic and environmental factors, plays a major role in MS pathophysiology. A more severe clinical course can be predicted by frequent relapses in the first 2 years, primary progressive form, male sex, and early permanent symptoms.

Current management/treatment

An increasing number of disease-modifying medications have become available in recent years, e.g., preparations of interferon beta; immune modulating monoclonal antibodies, chemotherapeutic agents, and several oral agents. It is beyond the scope of this fact sheet to discuss the relative benefits, risks, modes of action, and routes of administration of these medications, except to say that all shall reduce the likelihood of the development of new white-matter lesions, clinical relapses, and stepwise accumulation of disability. Based on the ability of several of these drugs to delay the diagnosis of MS after an initial attack, there has been a general move toward early treatment, although the long-term value of this approach with respect to preventing progressive MS remains uncertain. Azathioprine, cyclophosphamide, or intravenous immunoglobulins are no longer part of first line treatment. Standard treatment for CIS, or acute MS attacks or relapses in adult as well as pediatric patients without change is intravenous administration of high dose steroids. If patients are unresponsive, which occurs in 20-25%, after an interval of 10-14 days a second steroid pulse in combination with therapeutic apheresis is recommended.

Rationale for therapeutic apheresis

TPE or IA may benefit MS patients by the immediate removal of plasma antibodies and immune complexes, induction of a redistribution of antibodies from the extravascular space, and subsequent immunomodulatory changes. Early active MS lesions can be classified into four immunohistopathological patterns (Lucchinetti, 2000). Pattern II lesions are selectively associated with immunoglobulins and complement deposited along myelin sheaths, and predict the best response to TPE or IA. This was shown in patients with steroid-unresponsive relapse and availability of biopsies (Stork, 2018). However, clinical, radiographic, or biomarkers that reliably differentiate immunopathological patterns or disease mechanisms are not available. According to US and European recommendations TPE is indicated in acute, severe MS acute attacks or relapses with RRMS/SPMS not responsive to initial treatment with high-dose steroids (MSTCG, 2008). Overall results with RRMS are better compared to SPMS (Khatri, 2000; Magana, 2011). Clinical improvement may not be accompanied by resolution of active lesions on imaging. Use of IA in this setting has also been reported in multiple CS. Studies retrospectively evaluated 207 patients and observed >71% response rates suggesting a similar efficacy as TPE, thus preserving valuable plasma proteins and avoiding risks associated with substitution of human plasma products (Heigl, 2013; Schimrigk, 2016). Recovery of visual acuity in cases with optic neuritis was a prominent clinical result (Dorst, 2016; Koziolek, 2012). In pregnancy, available disease modifying therapies for MS are contraindicated. Steroid pulse therapy can have severe side effects for the embryo or the mother. In a recent retrospective analysis 83% of patients showed a marked improvement of relapse symptoms after IA during pregnancy or breastfeeding (Hoffmann, 2018). In contrast, TPE must be regarded as ineffective for the chronic phase of PPMS/SPMS based upon results of several RCTs (Cortese, 2011; Vamvakas, 1995). TPE or IA has been used for drug removal in MS patients treated with natalizumab who developed progressive multifocal leukoencephalopathy (see separate fact sheet).

Technical notes

Almost all studies on IA in MS used single-use tryptophan adsorbers.

Volume treated: 1-1.5 TPV with TPE; 2-2.5 liters for tryptophan-IA (manufacturer's recommendation); up to 2.5 TPV with regenerative immune adsorbers.	**Frequency:** Acute attack/relapse: 5-7 over 10-14 days; no recommendation for chronic phases of PPMS/SPMS.
Replacement fluid: TPE: albumin; IA: NA	

Duration and discontinuation/number of procedures

In acute MS attack/relapse unresponsive to steroids, 5-7 TPE or IA procedures have a response rate of >50%. Early initiation of therapy, within 14-20 days of onset of symptoms, is a predictor of response. However, response still occurred in patients treated 60 days after the onset of symptoms.

Keywords: multiple sclerosis, multiple sclerosis therapy, optic neuritis, plasma exchange, acute CNS demyelinating disease, immunoadsorption

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MYASTHENIA GRAVIS

Incidence: 3-28/million	Indication	Procedure	Recommendation	Category
	Acute, short-term treatment*	TPE/IA	Grade 1B	I
	Long-term treatment	TPE/IA	Grade 2B	II
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
TPE	10(394)	11(545)	NA	NA
IA	1(19)	5(131)	15(164)	NA

*Treatment recommendations are for moderate-severe disease including myasthenic crisis, unstable or refractory disease, unstable disease activity pre-thymectomy

Description of the disease

Myasthenia gravis (MG) is an autoimmune disease in which antibodies bind to acetylcholine receptors (AChR) or to functionally related molecules in the postsynaptic membrane at the neuromuscular junction and in skeletal muscle. The antibodies induce weakness of skeletal muscles, which can be generalized or localized, and nearly always includes eye muscles causing diplopia and ptosis. The weakness typically increases with exercise and repetitive muscle use. Ten percent of patients with MG have a thymoma. Two-thirds of patients with MG have generalized early-onset (cutoff age 50 years, female preference) or late-onset disease and no thymoma. Juvenile MG is defined as an onset before the age of 15. Rare cases of neonates were described, due to passive maternal antibody transfer. The diagnosis of MG is confirmed by the combination of typical symptoms, and a positive autoantibody test. Antibodies against AChR, muscle-specific kinase (MuSK, ~10%, often more severe MG), and lipoprotein receptor-related protein 4 (LRP4, 1-3%, less severe MG) are specific and sensitive for the detection of MG and define disease subgroups. Antibodies against titin, agrin, and ryanodine receptor may be suggestive of more severe disease. In antibody-negative cases (10-15%), neurophysiological tests and a characteristic response to therapy secure the diagnosis. Myasthenic crisis still represents a serious, life-threatening event characterized by rapid worsening of MG and potential airway compromise from ventilatory or bulbar dysfunction, requiring mechanical on non-invasive ventilation.

Current management/treatment

Increasing use of immunomodulating therapies has been a major factor in improving the prognosis for patients with MG, however, the current mortality of myasthenic crisis is still 2-3%. Therapy should be aimed at full or nearly full remission. Major treatment approaches include cholinesterase inhibitors, thymectomy, immunosuppression, and either therapeutic apheresis or IVIG. Acetylcholinesterase inhibition is the first line treatment for all MG subgroups. MG with MuSK antibodies generally has a less favorable response. Cholinergic side effects, including diarrhea, abdominal cramping, increased salivation, sweating and bradycardia, are dose limiting. Thymectomy results in clinical improvement and can reduce the need for immunosuppression. In early-onset MG it is best performed between ages 15-50 years. Current evidence does not support thymectomy in MG with MuSK or LRP4 antibodies. Immunosuppressive drugs for long-term management of MG are first-line corticosteroids, azathioprine, or mycophenolate, second-line cyclosporine, tacrolimus, or finally cyclophosphamide. Evidence of efficacy is mounting for rituximab, particularly in MuSK-MG. The complement inhibitor eculizumab received FDA and European approval for AChR-antibody positive generalized MG if immunosuppression failed.

Rationale for therapeutic apheresis

There are 3 major mechanisms of action for TPE, or IA in MG: immediate intravascular reduction of autoantibody concentration, pulsed induction of antibody redistribution, and subsequent immunomodulatory changes. Absolute autoantibody levels do not correlate with disease severity. However, a direct individual correlation of AChR-antibody decline with increasing muscle strength was shown with a series of IA treatments (Grob, 1995). Indications are myasthenic crisis; acute exacerbation of MG, particularly in patients with bulbar or severe generalized symptoms; and stabilizing the clinical state prior to thymectomy. In an RCT on thymectomy, TPE was used in 13% of patients to stabilize MG activity, and to improve postoperative outcome (Wolfe, 2016). In therapy refractory patients TPE or IA may represent an option for long-term management of MG (Sanders, 2016). Although no absolute consensus exists on the optimal schedule, studies have generally endorsed 3-6 treatments daily, or alternate daily exhibiting equivalent efficacy compared to IVIG with 60-70% improvement after 2 weeks. Notably, even treatment of plasma volumes below 1 TPV is effective in two thirds of patients with severe MG using TPE, or IA (Köhler, 2011; Trikha, 2007). IVIG and TPE are regarded as equally effective in treating severe MG (Gajdos, 2012). Comparative effectiveness was studied in large hospital patient data bases and demonstrated IVIG to be more cost effective (Mandawat, 2010). Since IVIG is a more convenient form of immunomodulatory treatment, it is often preferred over TPE. However, TPE was favored in patients with more severe respiratory impairment prior to initiating treatment. Accordingly, TPE was more effective if initiated earlier after hospital admission in severe cases (Mandawat, 2011). IA methods exhibited equal efficacy compared to TPE, thus avoiding replacement of human plasma products with their potential side effects or cost. DFPP was comparable to TPE with small pore plasma filters and procedural steps of rinsing, plasma discarding and substitution. TPE, or IA work rapidly, the clinical effect can be apparent within 24 hours but may take a week. Concomitant immunosuppression must be initiated or modified for sustained control of MG activity. Apheresis may be more effective than IVIG in patients with MuSK- MG.

Technical notes

Volume treated: 1-1.5 TPV with TPE; 2-2.5 liters for tryptophan-IA (manufacturer's recommendation); up to 2.5 TPV with regenerative immune adsorbers.

Frequency: Acute attack/relapse or unstable disease activity: 3-6 treatments over 10-14 days; weekly to bi-weekly individually adjusted for chronic treatment.

Replacement fluid: TPE: Albumin; IA: NA.

Duration and discontinuation/number of procedures

TPE, or IA are appropriate options as fast acting intervention to decrease MG activity. Actual number of procedures depends upon clinical scenario.

Keywords: myasthenia gravis, plasma exchange, immunoadsorption, thymectomy

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MYELOMA CAST NEPHROPATHY

Incidence: 1/100,000/yr		**Procedure**	**Recommendation**	**Category**
		TPE	Grade 2B	II
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	5(182)	1(29)	9(113)	NA

Description of the disease

Renal disease develops in up to 50% of patients with multiple myeloma and shortens their survival. Myeloma kidney (also known as cast nephropathy) accounts for about 30-80% of such cases, depending on the class of M-protein. Development of acute kidney injury is associated with poor 1-year survival. Autopsy studies show distal renal tubules obstructed by laminated casts composed of light chains (Bence-Jones protein), albumin, Tamm-Horsfall protein, and others. As tubular obstruction progresses the decline in renal function becomes irreversible. Hypotheses regarding the mechanism of pathological distal tubule cast formation focus on an increase in light chain concentration in the distal tubular urine. This may result from the overwhelming of proximal tubule processing of light chains when monoclonal free light chain (FLC) production is rising due to tumor progression, and co-precipitation of those light chains with Tamm-Horsfall protein (otherwise called uromodulin). Stimulation of nuclear factor κB (NFκB) pathways by tubular toxicity of free light chains may also contribute to intratubular obstruction. This can lead to interstitial nephritis and fibrosis. Other contributing factors may include hypercalcemia, hyperuricemia, dehydration, intravenous contrast media, and toxic effects of light chains on distal tubular epithelium.

Current management/treatment

Therapeutic approaches include general measures: discontinuing nephrotoxic medications, volume expansion with crystalloid solutions, avoiding diuretic medications, avoiding intravenous (IV) radiocontrast, monitoring serum calcium and uric acid levels, calcitonin for initial correction of severe hypercalcemia, bisphosphonate therapy, managing hyperuricemia, reducing urate formation by inhibiting xanthine oxidase activity, and converting urate to water-soluble allantoin (allopurinol, rasburicase). Supportive care with hemodialysis or peritoneal dialysis is employed as needed. The treatment of elevated serum FLCs include volume expansion with IV saline, chemotherapy consisting of an alkylating agent and corticosteroids are used to diminish M-protein production. More recently, immune modulation (thalidomide, lenalidomide), and especially proteasome inhibition (bortezomib) have emerged as highly effective therapy and are considered to be reno-protective. Routine measurement of serum FLC is highly recommended to assess treatment efficacy.

Rationale for therapeutic apheresis

TPE has been used to acutely decrease FLCs, since early reduction in FLCs have been associated with better renal outcomes and overall survival. A randomized trial of 21 patients with biopsy-proven myeloma kidney who received melphalan, prednisone, and forced diuresis with or without TPE showed no statistically significant outcome differences (Johnson, 1990). However, among a dialysis-dependent subgroup, 43% in the TPE group and none in the control group recovered renal function. Biopsy findings that indicated potential reversibility (e.g., absence of fibrosis of all affected glomeruli) were important predictors of success. This led to endorsement of TPE for myeloma kidney by the Scientific Advisors of the International Myeloma Foundation. The largest RCT of chemotherapy and supportive care (with 58 subjects receiving TPE and 39 controls) failed to demonstrate that 5-7 TPE procedures over 10 days substantially reduces a composite outcome of death, dialysis dependence, or estimated glomerular filtration rate of <30 mL/min/1.73m^2 at 6 months (Clark, 2005). This study has called into question TPE's role in the treatment of myeloma kidney in an era of rapidly effective chemotherapy. However, this study has been criticized principally because most of the enrolled patients were not proven to have cast nephropathy by renal biopsy and FLC levels were not measured. Survival at 6 months, which was similar in the TPE and control groups, has been questioned as part of the composite outcome, as opposed to end points more specific to recovery of renal function. For example, dialysis dependence in those who survived 6 months was 13% in TPE cases but 27% in controls; this difference was not statistically significant because of wide confidence intervals that suggest that the study was underpowered. Both the American Society of Nephrology Onco-Nephrology Forum and the Onconephrology Work Group of the Italian Society of Nephrology did not recommend plasma exchange as a treatment option for myeloma cast nephropathy. However, a Mayo Clinic CS restricted to patients with biopsy-proven cast nephropathy, showed that when TPE achieved a 50% reduction of FLC, then it was effective in reversing renal failure and extending survival (Leung, 2008). Based on a report of 14 patients with presumed myeloma cast nephropathy treated with bortezomib and TPE, 12 had complete or partial renal response by 6 months (Burnette, 2011). One controlled study in 29 patients with myeloma and acute kidney injury showed a significant decrease of FLCs in patients treated with TPE compared to the bortezomib group and there was a significantly higher decrease of FLCs and longer survival in patients treated with 3 or more TPEs than patients treated with 2 TPEs (Premuzic, 2018). Thus, it is believed by many that intensive TPE can improve outcomes if applied immediately with concurrent chemotherapy until blood FLC levels have been substantially reduced.

Technical notes

Published studies vary with respect to treatment schedules and replacement fluids employed for TPE. If TPE and hemodialysis are to be performed on the same day, they can be performed in tandem (simultaneously) without compromising the efficiency of the hemodialysis procedure.

Volume treated: 1-1.5 TPV	**Frequency:** Daily or every other day
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

CTs have employed TPE as a short-term adjunct to chemotherapy and fluid resuscitation over a period of 2-4 weeks. In some studies, a course of TPE (10-12 procedures over 2-3 weeks) may be repeated depending on the patient's clinical course.

Keywords: multiple myeloma, renal disease, apheresis, plasma exchange, cast nephropathy

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NEPHROGENIC SYSTEMIC FIBROSIS

Incidence: Rare		**Procedure**	**Recommendation**	**Category**
		ECP/TPE	Grade 2C	III
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
ECP	0	0	5(17)	4(5)
TPE	0	0	5(11)	2(3)

Description of the disease

Nephrogenic systemic fibrosis (NSF) is a rare but severe systemic disorder in patients with acute or chronic kidney disease (CKD), almost exclusively associated with the administration of gadolinium (Gd) containing contrast agents. It occurs in 3-7% of patients with renal insufficiency receiving galadoamide. Risk factors include patients with GFR <30 mL/min/1.73 m^2, patients with current thrombotic or inflammation, and the use of higher dose of Gd. It has not been reported in those with a GFR >60 mL/min/1.73m^2. NSF occurs also in patients with hepatorenal syndrome and in perioperative period following liver transplantation. Additional factors associated include surgery, systemic infections, metabolic acidosis, high erythropoietin levels, and elevations in calcium, iron, zinc, copper, and phosphate.

It usually takes 2-4 weeks between Gd administration and NSF onset; however, the range can be from 2 days to 8 years. Typical presentation involves the skin and consists of a symmetrical erythematous rash, non-pitting edema, paresthesias, and pruritus in the extremities. Additional findings include hair loss, gastroenteritis, conjunctivitis, bilateral pulmonary infiltrates, and fever. Over 6-12 months, swelling, pruritus, and sensory changes resolve while the skin progresses to thickened, hardened dermis/subcutis with epidermal atrophy. Fibrosis results in joint contractures leading to wheel-chair dependence and may extend into deeper tissues including skeletal muscle, heart, pericardium, pleura, lungs, diaphragm, esophagus, kidneys, and testes. In a small group of patients, disease progresses to death within weeks to months. Most patients experience a chronic and unremitting course with an overall mortality rate up to 30%. In a subgroup of patients with recovered renal function, the disease can enter remission.

The pathophysiology is unknown. Advanced kidney disease markedly prolongs Gd contrast excretion. Prolonged elimination results in disassociation of the Gd, which may be further enhanced by metabolic acidosis. Increased phosphate levels and inflammation lead to Gd phosphate tissue deposition. This is taken up by tissue macrophages resulting in pro-inflammatory and pro-fibrotic cytokine production leading to tissue infiltration by circulating CD34+ fibrocytes and collagen production. Gd may also directly stimulate fibroblasts. Multiorgan Gd deposition and fibrosis have been reported in autopsies.

Current management/treatment

There is no definite treatment besides reconstitution of renal function. Thus, renal transplant has been associated with cessation of progression and reversal in some patients. It should be noted that dialysis has not been associated with improvement once symptoms are established. Initiation of prophylactic hemodialysis shortly after exposure to Gd may decrease the likelihood of the harmful effect - one and three full sessions of dialysis can remove 97% and >99% of the dose, respectively. Additional therapies include IVIG, alefacept, pentoxifylline, imatinib messylate, chelation therapy with sodium thiosulfate, TPE, and ECP; however, all are associated with inconsistent clinical improvement. Steorids and cyclophosphamide are generally associated with no improvement. Avoidance of Gd administration, if possible, has been recommended for patients with GFR <30 mL/min/1.73 m^2.

Rationale for therapeutic apheresis

Due to the lack of an effective therapy and similarity between NSF and scleromyxedema, TPE has been applied. In the cases reported in the literature, patients demonstrated improvement including skin softening, increased range of motion (ROM), improved ambulation, and improvement from wheel-chair bound to walking. Additional reported changes include decreased swelling, pain, and paresthesias.

ECP has been applied to NSF because of similarities to symptoms of chronic graft versus host disease and scleromyxedema. In the reported cases, improvement includes skin softening, increased ROM, improved ambulation, and improvement from being wheel chair bound to walking. Additional reported changes include resolution of skin lesions and decreased pruritus.

Technical notes

Relationship between time of initiation of therapy and reversal of changes is unclear. Whether the changes become irreversible or if earlier treatment is more effective than later has not been determined.

Volume treated: ECP: Typically, MNCs are obtained from processing 1.5L of whole blood, but volume processed varies based on patient weight and HCT. 2-process method collects and treats MNCs obtained from processing 2 TBV; TPE: 1-1.5 TPV

Frequency: ECP: Various schedules ranging from 2 in consecutive days every 2-4 weeks up to 5 procedures every other day (cycle) with increasing number of weeks between cycles (1 to 4) with 4 cycles composing a round; TPE: Various schedules ranging from daily for 5 treatments to twice per week for 10 - 14 treatments

Replacement fluid: ECP: NA; TPE: albumin

Duration and discontinuation/number of procedures

Time to response has not been reported for most patients treated with TPE. Improvement of early symptoms in one patient reported to have occurred within 3 days of treatment initiation. Time to response with ECP ranged from 4-16 months.

Keywords: Nephrogenic systemic fibrosis, plasma exchange, extracorporeal photopheresis, gadolinium

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NEUROMYELITIS OPTICA SPECTRUM DISORDERS (NMOSD)

Incidence: <1/100,000		**Indication**	**Procedure**	**Recommendation**	**Category**
		Acute attack/relapse	TPE	Grade 1B	II
			IA	Grace 1C	II
		Maintenance	TPE	Grade 2C	III
# reported patients: >300		**RCT**	**CT**	**CS**	**CR**
Acute attack/relapse	TPE	0	3(154)	18(274)	NA
	IA	0	0	2(17)	8(10)
Maintenance	TPE	0	0	1(7)	1(2)

Description of the disease

Neuromyelitis optica (NMO or Devic's disease) is an inflammatory CNS syndrome, a distinct disease entity from multiple sclerosis, that is associated with serum aquaporin-4 immunoglobulin G antibodies (AQP4-IgG). Prior NMO diagnostic criteria required optic nerve and spinal cord involvement but more restricted or more extensive CNS involvement may occur. Current nomenclature defines the unifying term NMO spectrum disorders (NMOSD), which is stratified further by serologic testing (NMOSD with or without AQP4-IgG). The core clinical characteristics required for patients with NMOSD with AQP4-IgG include clinical syndromes or magnetic resonance imaging findings related to optic nerve (optic neuritis, ON), spinal cord (longitudinally extensive transverse myelitis, LETM), area postrema, other brainstem, diencephalic, or cerebral presentations typically manifesting as acute attacks. More stringent clinical criteria, with additional neuroimaging findings, are required for diagnosis of NMOSD without AQP4-IgG or when serologic testing is unavailable. At least two core clinical criteria must be present, one of which must be ON or LETM, imaging consistent with NMO, and no alternative explanation for symptoms. It is important to note, that ON alone can have many different underlying etiologies. Several clinical features highly distinctive for NMO and NMOSD have been identified, which include simultaneous LETM, with potential respiratory failure, and ON, bilateral ON, and intractable nausea with hiccups and vomiting. Furthermore, NMO and NMOSD can be associated with myopathy and occur in the context of systemic autoimmune disease or cancer.

Autoantibodies against aquaporin-4 (AQP4-IgG), the principal water channel on astrocyte foot processes at the blood brain barrier, are pathogenic in NMOSD. IgG binding to AQP4 leads to complement-dependent astrocyte cytotoxicity, leukocyte infiltration, cytokine release, and blood-brain barrier disruption, resulting in oligodendrocyte death, myelin loss and neuron death. AQP4-IgG are found in approximately 70% of patients. Antibodies to myelin oligodendrocyte glycoprotein (MOG-IgG) are a marker of autoimmune ON and often LETM. Since AQP4-IgG is usually absent in MOG-IgG-positive patients, that the histopathology of inflammatory CNS lesions differs between MOG-IgG- and AQP4-IgG-positive patients, and that MOG-IgG are pathogenic both in vitro and in vivo, MOG-IgG-related autoimmunity is now considered by many a disease entity distinct both from classical MS and from AQP4-IgG-mediated NMOSD. Extra-opticospinal manifestations in MOG-IgG related autoimmunity are not yet fully understood.

NMOSD can have either a monophasic or relapsing course. Monophasic course is associated with younger age at disease onset and equal male: female predominance. Monophasic course has 90% 5-year survival rate. Approximately 90% of patients with NMOSD have relapsing course, which has a poor prognosis: 50% of patients become legally blind or wheelchair bound and 30% die of respiratory failure within 5 years. The disease worsens by incomplete recovery with each acute attack.

Current management/treatment

Acute attacks are managed by high-dose intravenous methylprednisolone, 1g daily for 3-5 days, followed by oral taper and, if symptoms fail to resolve, TPE or IA is added. Prophylaxis to prevent further acute attacks includes immunosuppressive medications and immunomodulation, such as oral steroids, azathioprine or mycophenolate mofetil, methotrexate, cyclosporine A or tacrolimus, cyclophosphamide, IVIG, rituximab, tocilizumab and eculizumab, either alone or in combination therapies. Individual decision making with highly specialized neurologists is beneficial.

Rationale for therapeutic apheresis

Several CRs have shown TPE benefits in corticosteroid-refractory NMOSD exacerbation. One clinical trial showed TPE added to pulsed intravenous corticosteroids is more effective than pulsed intravenous corticosteroids alone (Merle, 2012). Although mostly given as escalation therapies, TPE or IA can be considered initial treatment for severe attacks, in particular when previous attacks have responded well to apheresis therapies but not to steroids. Prompt initiation of TPE is a strong predictor of beneficial outcome in severe attacks of NMOSD; for every day delayed in initiation of therapy, the odds of achieving complete remission are reduced by 6.3% (Kleiter 2018).

There have been several reports using IA to treat patients with acute NMOSD. In one study, 10 patients received an average of 5 IA procedures (range 3-7), in addition to immunosuppressive therapy (Faissner, 2016). All 10 patients demonstrated an amelioration of admission symptoms after IA. Isolated myelitis responded better to TPE or IA compared to high-dose pulsed intravenous corticosteroids as first treatment course (Kleiter, 2016A). In 2018, the Neuromyelitis Optica Study Group published a retrospective study of 105 patients with NMOSD who were treated with TPE or IA. There was no significant difference in efficacy between the two groups. The strongest predictors of complete remission were use of apheresis as first-line therapy, time from onset of attack to start of apheresis therapy, and presence of AQP4-IgG (Kleiter, 2018). In addition, retrospective reviews have shown that TPE may be beneficial as a chronic treatment for the prevention of NMOSD relapse in select patients.

Technical notes

Volume treated: TPE: 1-1.5 TPV; IA: 2-2.5 liters for tryptophan-IA (manufacturer's recommendation); up to 2.5 TPV with regenerative immune adsorbers

Frequency: Acute attack/relapse: daily or every other day. Individually adjusted intervals for maintenance treatment.

Replacement fluid: Albumin

Duration and discontinuation/number of procedures

The majority of studies performed 5 procedures on average for acute exacerbation but ranged from 2-20 procedures. Early initiation of apheresis (≤ 5 days since clinical onset) was recommended (Bonnan, 2018). In one CS, 5 out of 7 patients who were on maintenance TPE therapy (3 per week for 2 weeks, 2 per week for 2 weeks, then weekly for 3 to 5 weeks) showed varying degrees of improvement and reduction in the number of NMOSD exacerbations.

Keywords: Neuromyelitis optica, Neuromyelitis Optica Spectrum Disorders, plasma exchange, immunoadsorption, Devic's disease, optic neuritis

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N-METHYL-D-ASPARTATE RECEPTOR ANTIBODY ENCEPHALITIS

Incidence: Rare		**Procedure**	**Recommendation**	**Category**
		TPE/IA	Grade 1C	I
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	0	1(21)	34(447)	NA

Description of the disease

N-methyl D-aspartate receptor (NMDAR) encephalitis is the most common form of autoimmune antibody mediated encephalitides (Dalmau, 2018). This group of acute inflammatory brain disorders is characterized by prominent neuropsychiatric symptoms and are associated with antibodies against neuronal cell-surface proteins, ion channels, or receptors. NMDAR-encephalitis is characterized by IgG antibodies targeting subunits of the NMDAR. NMDAR encephalitis typically affects children and young adults, with a female predominance. Up to 58% of affected young female patients have an ovarian teratoma. Young children typically present with insomnia, seizures, abnormal movements, or variable changes in behavior. Teenagers and adults more often present with psychiatric symptoms, including agitation, hallucinations, delusions, and catatonia. The disease progresses in a period of days or weeks to include reduction of speech, memory deficit, orofacial and limb dyskinesias, seizures, decreased level of consciousness, and autonomic symptoms like excess salivation, hyperthermia, fluctuations of blood pressure, tachy- or bradycardia, or central hypoventilation. One month after disease onset most patients have a syndrome that combines several of the above-mentioned symptoms. Occurrence as autoimmune sequelae after herpes simplex virus encephalitis must also be considered (Schein, 2017). If the impairment of autonomic functions progresses, the disease can be fatal. Mortality is in the range of 4%. Definitive diagnosis can be made by the detection of NMDAR antibodies most specifically in the cerebrospinal fluid (CSF), in serum false negative results are more frequent. Magnetic resonance imaging of the brain is abnormal in only 30% of patients. Delay in diagnosis is common as NMDAR encephalitis is often mistaken for psychosis or viral encephalitis.

Current management/treatment

Once diagnosed, immunotherapy should be promptly initiated. First-line therapy includes high dose corticosteroids, IVIG, or TPE/IA, and a search for potential underlying tumor. Early initiation of immunotherapy is a strong predictor of favourable outcome after 12 months, especially in children. In cases with associated tumor, optimal response to immunotherapy is contingent upon tumor removal. Approximately 50% of patients respond to these immunotherapies; the other 50% require additional therapies, such as rituximab or cyclophosphamide. In severe refractory cases bortezomib has been successfully used to induce remission and repeated pulsed corticosteroids to maintain remission (Scheibe, 2017). Approximately 80% of patients recover or improve at 24 months (approximately 50% within 4 weeks); in 20% residual deficits remain. Recovery is gradual and symptoms begin disappearing in reverse order of appearance. Relapses occur in 12-20% of cases. Patients who do not respond to treatment, or who have relapses, should be reassessed for the presence of an underlying still undetected or recurrent teratoma. Disease activity appears to correlate with antibody levels e.g., decreased or undetectable during remission, and increased with relapse thus, making quantitation of autoantibodies helpful for patient management and monitoring response to immunotherapy. Psychopharmacological treatment is often necessary for the management of psychiatric symptoms.

Rationale for therapeutic apheresis

TPE removes the pathophysiologically relevant antibody, an adjunct to immunotherapy for suppressing active inflammation and antibody production. Teratoma excision, if present, is necessary for removing the possible antibody stimulus. There is a substantial percentage of patients with anti-NMDAR encephalitis who do not respond to TPE. Nevertheless, TPE remains among the treatment options and is included in the treatment recommendations from the German Network for Research on Autoimmune Encephalitis. The evidence for using TPE in autoimmune encephalitis is limited to CS or CRs. Although NMDAR is an extracellular antibody, as in most autoimmune encephalitides, antibody production and inflammatory changes occur behind the blood-brain barrier, which probably explains the lower effectiveness of TPE this disorder, compared to systemic antibody mediated disease (Dalmau, 2018). There is no broad consensus about the exact order to apply corticosteroids, IVIG, or TPE, or when to initiate treatment with a combined multimodal approach. Systematic comparisons between the modalities are unavailable. CS suggest early initiation of TPE or TPE followed by IVIG, provide better outcomes. Furthermore, fewer patients showed improvement following corticosteroids as compared to corticosteroids immediately followed by TPE (DeSena, 2015).

IA was used in two CS mostly after an initial steroid pulse in 32 patients with antibody-associated encephalitis (16 anti-NMDAR; Dogan-Onugoren, 2016; Köhler, 2015). After 5-10 IA treatments clinical improvement was noted in most patients. In a small prospective case control study including 21 patients with antibody-associated encephalitis, TPE (5-12 treatments) was compared with IA (3-7 treatments) (Heine, 2016). Both apheresis modalities showed equal efficacy with 60-70% of patients improving, and suggesting fewer side effects with IA.

Technical notes

Volume treated: TPE: 1-1.5 TPV; IA: 2-2.5 liters for tryptophan-IA (manufacturer's recommendation) or up to 2.5 TPV with regenerative immune adsorbers	**Frequency:** 5-12 treatments with TPE or IA over 1-3 weeks with individually adjusted number of and intervals between treatments
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

IgG antibody needs to equilibrate between the intravascular and extravascular spaces, in anti-NMDAR encephalitis, also between plasma and CSF. With IA, CSF antibody titers were reduced by 66% at early follow-up (Dogan-Onugoren, 2016). Long periods of hospitalization may be required with tentative repetition of a series of TPE, or IA. Patients reported in the literature did not always improve rapidly after the completion of a course of TPE or IA.

Keywords: *N*-methyl-D-aspartate receptor, autoimmune encephalitis, plasma exchange, immunoadsorption

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OVERDOSE, ENVENOMATION, AND POISONING

Incidence: Rare	**Indication**	**Procedure**	**Recommendation**	**Category**
	Mushroom poisoning	TPE	Grade 2C	II
	Envenomation	TPE	Grade 2C	III
	Drug overdose/poisoning	TPE	Grade 2C	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Mushroom poisoning	0	1(23)	1(305)	NA
Envenomation	0	0	3(77)	NA
Drug overdose/poisoning	0	0	12(215)	NA

Description of the disease

Drug overdose (accidental, intentional, or iatrogenic), envenomation, or poisoning result from exposure to agents or toxins capable of producing tissue injury and/or organ dysfunction. Ingestion, inhalation, and injection are common routes of exposure for drugs and poisons. Envenomation occurs from snakes, spiders, scorpions, or venomous stinging insects. The list of agents potentially toxic to humans is enormous and diverse. It is difficult to quantify the morbidity and mortality attributable to these problems. Most poisoning incidents are accidental and occur at home, most often involving children <6 years. Fortunately, serious injury is the exception, not the rule. The mechanism of tissue damage varies with the nature of the offending substance and the mode of entrance into the body. Agents may be directly toxic to human tissue or may require enzymatic conversion to an active, injurious metabolite. Local effects at the site of entry into the body may accompany systemic effects, and the onset of symptoms may be rapid or delayed. Initial treatment focuses on supportive care and the removal of the toxic agent.

Current management/treatment

Evaluation and stabilization of the airway, breathing, circulation, and neurologic status are primary concerns. Toxin-specific antidotes or anti-venoms, when available, are promptly administered. Induced emesis, gastric lavage, and oral administration of activated charcoal may be used to minimize gastrointestinal absorption of ingested substances. Whole-bowel irrigation, another technique available for gastro-intestinal decontamination, is particularly useful for removing poorly absorbed agents that are not adsorbed to charcoal. Forced acid or alkaline diuresis is used to promote the renal elimination of ionized agents that are not strongly bound to proteins. Hemodialysis is an effective technique for removing drugs that are not tightly bound to plasma proteins and that readily diffuse through a semipermeable membrane. Hemoperfusion, a procedure in which blood is passed directly over sorbent particles, can be more effective than dialysis for protein-bound drugs and large molecules.

Rationale for therapeutic apheresis

Amanita mushroom poisoning is the most frequent clinical diagnosis where TPE has been utilized, in addition to other therapies to remove toxin including activated charcoal and forced diuresis. Large CS showed decreased mortality among patients, mostly children, treated with TPE when compared with historical controls. Very early initiation of the treatment (within the first 24-48 hours) is recommended. Other environmental exposures where the use of TPE has been described include castor bean ingestion and pesticide/organophosphate poisoning.

TPE has also been used for toxin removal following envenomation from snake or brown recluse spider bites and scorpion or Africanized bee stings. A published CS described 37 patients treated with TPE following snake bite when limb swelling did not improve following anti-venom administration and supportive care. All patients survived to discharge with limb preservation (Zengin, 2013).

Reports of the successful use of apheresis in the treatment of various drug overdoses and poisonings are based only on CRs and CS (Schutt, 2012). TPE may be used for the removal of drugs with a low volume of distribution (<0.2 L/ kg) and/or high-plasma protein binding (>80%). Other important factors include the time between dose administration and TPE initiation and the relationship between the amount of drug removed and the biologic effect. The effect of TPE on the removal of various drug classes has been described (Ibrahim, 2013). Some medications have affinity to RBCs (e.g., tacrolimus) and RBC exchange has been successfully tried under those circumstances for a severe case of tacrolimus toxicity.

Technical notes

The replacement fluid chosen should be one that contains enough protein to draw toxin into the blood compartment for elimination; albumin is such an agent and generally acts as an effective replacement fluid. However, some toxic substances may bind to other plasma constituents preferentially over albumin. For example, dipyridamole, quinidine, imipramine, propranolol, and chlorpromazine are known to have strong affinity for alpha-1-acid glycoprotein; for overdoses of these agents, plasma may be a more appropriate choice. Some venoms also cause coagulopathy and possibly microangiopathy with low levels of ADAMTS13 (Ho, 2010), in which case the use of plasma should be strongly considered.

Volume treated: 1 - 2 TPV	**Frequency:** Daily
Replacement fluid: Albumin, plasma	

Duration and discontinuation/number of procedures

TPE is usually performed daily until the clinical symptoms have abated and delayed release of toxin from tissues is no longer problematic.

Keywords: Amanita mushroom, venom, envenomation, poisoning, toxins, overdose, plasma exchange

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PARANEOPLASTIC NEUROLOGICAL SYNDROMES

Incidence: Rare		**Procedure**	**Recommendation**	**Category**
		TPE/IA	Grade 2C	III
# reported patients: 100-300	**RCT**	**CT**	**CS**	**CR**
TPE	0	1(20)	12(104)	NA
IA	0	0	1(13)	1(1)

Description of the disease

The paraneoplastic neurologic syndromes (PNS) are a varied group of cancer-related neurologic disorders that are associated with onconeural antibodies (ON-Abs). Those antibodies target antigens that are expressed by both the tumor and the nervous system and mainly recognize intracellular antigens (e.g., Hu, CV2/collapsing response mediator protein 5 (CRMP5), Yo, Tr, and amphiphysin). Since the ON-Abs are directed against intracellular antigens, which are not directly accessible to the antibodies, it is presumed that the main pathogenic effect is most probably carried out by cytotoxic T cell mediated immune reactions, resulting in neuronal cell death. Many additional antibodies against cell surface or synaptic proteins (e.g., NMDAR, VGKC) associated with paraneoplastic syndromes of the central and peripheral nervous systems and the neuromuscular junction have been described and are reviewed under specific separate fact sheets. PNS is rare, occurring in 0.1-1% of cancer patients. Classical PNS manifestations are subacute cerebellar degeneration (or paraneoplastic cerebellar degeneration (PCD) which is the most common PNS syndrome), limbic encephalitis (LE), paraneoplastic encephalomyelitis (PEM), opsoclonus-myoclonus syndrome (OMS), which is the most common pediatric PNS, subacute sensory neuropathy (SSN), chronic gastrointestinal pseudo-obstruction, Lambert-Eaton myasthenic syndrome (LEMS; see separate fact sheet), and dermatomyositis.

The tumors most commonly associated with PNS are those that express neuroendocrine proteins, such as small cell lung cancer (SCLC), ovary, breast, or other gynecological malignancies; tumors that contain nervous tissue, such as teratomas; and tumors that affect organs with immunoregulatory functions, such as thymoma. PNS mostly precede detection of the underlying cancer; patients in whom PNS is strongly suspected but no cancer is identified should undergo periodic cancer screening for at least 5 years.

The diagnostic work-up of a suspected PNS includes proving its immune-mediated nature and ruling out meningeal disease, metastasis, and toxic or metabolic causes. If clinical suspicion of PNS remains high, screening for relevant ON-Abs should be initiated. Their presence or absence helps to further predict the probability and location of underlying cancer. Finally, a tumor screening guided by the clinical information and antibody status should be performed as the frequency, age dependency, and most probable tumor localization are suggested by the clinical syndrome and/or detected antibody.

Detecting ON-Abs, together with a compatible neurological syndrome, has a high specificity for PNS. However, even in patients with definite PNS in a large European network study, only 80% harbored ON-Abs. It has been reported that 60% of PNS of the central nervous system and <20% of those affecting the peripheral nervous system are associated with these antibodies.

Current management/treatment

Treatment of PNS includes antitumor and immunosuppressive therapy. Prompt initiation of anti-tumor therapy upon diagnosis can stabilize symptoms. If symptoms do not stabilize or if no tumor is detected, immunosuppression (usually steroids, TPE, IVIG, or IA) is tried. Aggressive immunosuppression early in the course is recommended in patients who are identified prior to a tumor diagnosis. IVIG (0.5 g/kg/day for 5 days every 4 weeks for 3 months, followed by 0.5 g/kg one day per month for another 3 months) may result in improvement in patients with anti-Hu or anti-Yo, mostly in those whose symptoms are restricted to the peripheral nervous system.

Rationale for therapeutic apheresis

The association of syndromes with specific cerebrospinal fluid and serum antibodies led to the use of immunosuppressive therapy, including TPE and IA. Most patients treated with TPE have also received immunosuppressive drugs as well as anti-cancer therapy. If a patient presents prior to development of severe neurological impairment but with a rapidly developing syndrome, aggressive immunosuppression, including TPE may be reasonable in an attempt to halt the process. Patients with subacute cerebellar degeneration or PCD with anti-Tr antibodies may be more likely to respond to TPE, though many of them do not have malignancy. TPE has not been shown to be effective in syndromes with ON-Abs, e.g., anti-Hu, anti-Yo as they do not target the cell-mediated autoimmunity directly. A CS of 13 patients with OMS or subacute cerebellar degeneration were treated with staphylococcal protein A IA (Batchelor, 1998). There were 3 complete and 3 partial neurological remissions; all subsequently relapsed. Although the exact mechanism of action of protein A IA is not well understood, data suggest that it results in a reduction of circulating IgG antibodies and immune complexes and an increase in natural killer cell activity.

Technical notes

Volume treated: TPE: 1-1.5 TPV; IA: 2 - 4 TPV	**Frequency:** TPE: Daily or every other day**;** IA: Twice weekly
Replacement fluid: TPE: Albumin; IA: NA	

Duration and discontinuation/number of procedures

TPE: 5-6 procedures over up to 2 weeks. In one reported clinical study patients were treated with Protein A IA twice weekly for 3 weeks (Batchelor, 1998).

Keywords: Paraneoplastic neurologic syndromes, onconeural antibodies, subacute cerebellar degeneration, limbic encephalitis, paraneoplastic encephalomyelitis, opsoclonus-myoclonus syndrome, plasma exchange, immunoadsorption

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PARAPROTEINEMIC DEMYELINATING NEUROPATHIES; CHRONIC ACQUIRED DEMYELINATING POLYNEUROPATHIES

Incidence: MGUS: <3% of age >50 yr; Anti-MAG neuropathy, MMN: rare	**Indication**	**Procedure**	**Recommendation**	**Category**
	IgG/IgA/IgM	TPE	Grade 1B	I
	Anti-MAG neuropathy	TPE	Grade 1C	III
	Multiple myeloma	TPE	Grade 2C	III
	MMN	TPE	Grade 1C	IV
# reported patients: 100-300	**RCT**	**CT**	**CS**	**CR**
IgG/IgA/IgM	1(39)	0	9(131)	NA
Anti-MAG* neuropathy	0	0	2(23)	0
Multiple myeloma	0	0	1(4)	1(1)
MMN	0	0	1(7)	8(10)

*Not inclusive, due to change of disease definition in later studies.
MGUS = monoclonal gammopathy of undetermined significance; MMN = multifocal motor neuropathy; MAG = myelin-associated glycoprotein

Description of the disease

Coexistence of neuropathy and monoclonal gammopathy is a common clinical problem. Polyneuropathy can present as an acute, subacute, or chronic process with initial sensory symptoms of tingling, prickling, burning or band-like dysaesthesias in balls of the feet or tips of toes, usually symmetric and graded distally. Nerve fibers are affected according to axon length, without regard to root or nerve trunk distribution (stocking-glove distribution). Polyneuropathies are diverse in time of onset, severity, mix of sensory and motor features, and presence or absence of positive symptoms. IgA and IgG monoclonal gammopathy can be associated with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP, see separate fact sheet), POEMS syndrome, and other neuropathic syndromes associated with monoclonal gammopathy.

Chronic acquired demyelinating polyneuropathies (CADP), a newer disease classification, include a variety of neuromuscular disorders resulting from immune-mediated demyelination: CIDP, multifocal motor neuropathy (MMN), multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), neuropathy associated with monoclonal IgM antibodies to myelin-associated glycoprotein (MAG; anti-MAG neuropathy), POEMS syndrome, and other neuropathic syndromes associated with monoclonal gammopathy. The classification of CADP takes into consideration both disease presentation and pathological etiology, thus better defines effective treatment. CIDP is discussed as a separate fact sheet in this edition, while POEMS is a Category IV indication for apheresis and is presented as a fact sheet in the JCA 2013 Special Edition. The diagnosis algorithm is first based on the presence of either motor or sensorimotor neuropathy. For patients with motor neuropathy, a combination of conduction block and demyelination would lead to the diagnosis of MMN. For patients with sensorimotor neuropathy, after confirmation of demyelination, further classification is based on antibody specificity. Typical presentation of MMN includes chronic asymmetric distal-limb weakness, atrophy and fasciculation that affect distal arm more frequently than leg; usually follows peripheral nerve distribution with limited or no sensory symptoms. It occurs in males > females, often in the fifth decade of life. Although resembling MMN, MADSAM is separate disease, a multifocal inflammatory demyelinating polyneuropathy, and is considered by some as a multifocal variant of CIDP. Once MMN is ruled out, the detection of anti-MAG in IgM monoclonal gammopathy associated neuropathy establishes the diagnosis of anti-MAG neuropathy. Typical presentation of anti-MAG neuropathy includes distal, predominantly sensory large fiber ataxic neuropathy, some patients may also have neurogenic tremor in the arms. In addition to anti-MAG, sulfated glucuronyl paragloboside antibodies may also be detected. Disease progression is variable, some may take years or decades and others may have acute accelerations. Anti-MAG neuropathy is associated with monoclonal gammopathy of undetermined significance (MGUS), but in 12-35% of cases, it is associated with Waldenström macroglobulinemia or B cell lymphoma.

Current management/treatment

The optimal treatment regimen is not clear. Response to immunosuppressive drugs varies. A large meta-analysis suggests limited support for the use of TPE, cyclophosphamide combined with prednisolone, IVIG, and corticosteroids for IgG and IgA paraproteinemic neuropathies (Stork, 2015). For MMN patients, a combination of corticosteroids and TPE may result in variable response, from partial and transient response, no response, to possible aggravation of the neuropathy. Cyclophosphamide has been used and can lead to transient improvement, but its use is limited by its toxicity. Response to IVIG is typically seen within several days and may last several weeks to months. IVIG has also been used for the prevention of disease progression.

Based on a comprehensive meta-analysis of IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies, the authors concluded that there is inadequate reliable evidence from trials of immunotherapies in anti-MAG paraproteinemic neuropathy in support of any particular treatment (Lunn, 2016). IVIG and rituximab are the most frequently used medications in this disorder. In one RCT with 26 patients, patients who received rituximab had significant improvement in the 'time to walk 10 meters' than in the placebo group (Dalakas, 2009). Another trial in 54 patients failed to reach the primary endpoint but did show improvements in several secondary outcomes (Leger, 2013). Clinical improvement is often seen when there is at least a 50% reduction of serum IgM.

Rationale for therapeutic apheresis

The rationale for using TPE is to remove anti-MAG or other antibodies. It is suggested that TPE is probably more effective for IgA and IgG MGUS-associated polyneuropathy, and not for IgM-MGUS (Cortese, 2011). For anti-MAG neuropathy, TPE may have a transient response. In one report, of

19 patients who had anti-MAG neuropathy (although some of them had abnormal conduction velocities) and received TPE, 40% had a transient effect, but most of them had a relapse upon stopping TPE (Gorson, 2001). Currently more effective treatments are available for MMN and anti-MAG neuropathy, TPE is rarely indicated for these conditions.

Technical notes

Volume treated: 1-1.5 TPV	**Frequency:** See below
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

Typical course is 5-6 treatments over 10-14 days with regimen being guided by clinical symptomatology.

Keywords: paraproteinemic polyneuropathy, neuropathy, polyneuropathy, paraproteinemic demyelinating neuropathies, chronic acquired demyelinating polyneuropathies, plasma exchange

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PEDIATRIC AUTOIMMUNE NEUROPSYCHIATRIC DISORDERS ASSOCIATED WITH STREPTOCOCCAL INFECTIONS (PANDAS); SYDENHAM'S CHOREA

Incidence: PANDAS: unknown; SC: 10-50% of ARF patients	**Indication**	**Procedure**	**Recommendation**	**Category**
	PANDAS, exacerbation	TPE	Grade 1B	II
	SC, severe	TPE	Grade 2B	III
# reported patients: 100-300	**RCT**	**CT**	**CS**	**CR**
PANDAS	1(29)	0	2(60)	7(7)
SC	1(18)	0	0	1(1)

PANDAS = pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; SC = Sydenham's chorea; ARF = acute rheumatic fever

Description of the disease

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and Sydenham's chorea (SC) are both pediatric post-infectious autoimmune neuropsychiatric disorders associated with Group-A beta-hemolytic streptococcus (GABHS) infection. SC, a neuropsychiatric manifestation of acute rheumatic fever (ARF), occurs in an estimated 10-50% of patients with ARF, is self-limiting and typically resolves after 3-18 months but recurrence may be more common than previously appreciated (up to 40%). The major clinical manifestations include involuntary choreoathetoid movements, hypotonia and emotional lability. Neuropsychiatric symptoms in the absence of ARF may represent PANDAS, a disease entity first described in 50 children (Swedo, 1998). The 5 diagnostic criteria proposed for PANDAS include: 1) presence of obsessive-compulsive disorder (OCD) and/or a tic disorder, 2) prepubertal onset, 3) abrupt onset or exacerbation of symptoms with an episodic (relapsing-remitting) course, 4) temporal association of symptoms with GABHS infection, and 5) association with neurological abnormalities including choreiform movements. A diagnosis of PANDAS may only be made after SC and ARF have been excluded as a cause of a child's symptoms. The onset of PANDAS is acute. The major clinical manifestations of PANDAS include obsessions, compulsions and tics often associated with co-morbid neuropsychiatric symptoms, including mood lability, attention deficit-hyperactivity disorder, separation anxiety, tactile/sensory defensiveness, enuresis, and catatonia. Severe symptoms often last several weeks to months or longer and then gradually subside. The peak age of onset for PANDAS and SC are 6-7 years and 8-9 years, respectively, with male predominance in PANDAS (3:1) and female predominance in SC (2:1). No laboratory tests are specific for the diagnosis and differentiation of PANDAS and SC. Evidence of GABHS infection through throat culture and/or an elevated or increasing antistreptococcal antibody titer [e.g., anti-streptolysin O (ASO)] supports the diagnosis of both. Elevated levels of anti-neuronal antibodies and/or anti-basal ganglia antibodies have been reported in both entities. Magnetic resonance imaging studies have demonstrated striatal enlargement in the basal ganglia in both, especially in caudate, putamen, and globus pallidus.

Current management/treatment

Initial treatments for PANDAS include cognitive behavioral therapy and/or anti-obsessional medications. Prompt antibiotic administration is indicated in patients with PANDAS with tonsillo-pharyngitis and a positive GABHS throat culture. In a double blind RCT, penicillin and azithromycin prophylaxis were found to be effective in decreasing streptococcal infections and neuropsychiatric symptom exacerbations in children with PANDAS (Snider, 2005). Tonsillectomy may represent an effective prophylactic treatment option in PANDAS patients, if clinically indicated. The severe form of SC is treated with diazepam, valproic acid, carbamazepine, or haloperidol. If these fail, corticosteroids may be tried. Unlike in PANDAS, children with SC require long-term penicillin prophylaxis to reduce the risk of rheumatic carditis. In severely symptomatic patients with PANDAS or SC, immunomodulatory therapies, such as IVIG (1 g/kg/d for 2 days) or TPE, have been shown to be effective in reducing symptom severity or shortening disease course (Vitaliti, 2015).

Rationale for therapeutic apheresis

Because of the possible role of anti-neuronal antibodies in the pathogenesis, antibody removal by TPE may be effective. An RCT of IVIG compared to TPE on 29 children with PANDAS showed that both therapies at one-month post treatment produced striking improvements in OCD, with mean improvement of 45% and 58%, respectively, as well as improvement in anxiety and overall function (Perlmutter, 1999). This effect appeared to be sustained on one-year follow up. The TPE group appeared to have greater tic symptom relief than did the IVIG group. In a recent large retrospective CS of TPE in 35 patients with PANDAS, patients showed significant improvement in symptoms after both short and long-term follow up. In this study, surprisingly, the duration of illness preceding TPE was not correlated with degree of improvement (Latimer, 2015). A randomized controlled study on 18 patients with SC showed that the mean chorea severity scores decreased by 72%, 50%, and 29% in the IVIG, TPE, and steroid groups, respectively, suggesting IVIG/TPE-mediated benefit, however these differences did not reach statistical significance (Garvey, 2005).

Technical notes

Volume treated: 1-1.5 TPV	**Frequency:** Daily or every other day
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

Three to 6 procedures performed over 1-2 weeks. There is limited data on benefit of repeat TPE treatment courses.

Keywords: PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, Sydenham's chorea, Group-A beta-hemolytic streptococcus, plasma exchange

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PEMPHIGUS VULGARIS

Incidence: <1/100,000/yr (US)	Indication	Procedure	Recommendation	Category
	Severe	TPE	Grade 2B	III
	Severe	ECP/IA	Grade 2C	III
# reported patients: 100-300	**RCT**	**CT**	**CS**	**CR**
TPE	1(40)	0	8(87)	13(13)
ECP	0	0	1(4)	7(11)
IA	0	1(6)	6(35)	5(5)

Description of the disease

Pemphigus vulgaris is a rare, potentially fatal, autoimmune mucocutaneous blistering disease. Genders are equally affected with typical age of onset 60-80 years. Patients present with skin lesions, recurrent and relapsing flaccid blisters, which are located on epidermal or mucosal surface. The lesions peel superficially or detach easily. A large surface of skin can be affected leading to situations akin to severe burn. Pathology of pemphigus vulgaris is characterized by the in vivo deposition of autoantibody, directed against Dsg 1 and 3 (desmoglein 1 and 3), on the keratinocyte cell surface. Histology reveals the presence of a suprabasilar intraepidermal split with acantholysis. There are deposits of IgG and C3 on the corticokeratinocyte cell surface in the mid and lower or entire epidermis of perilesional skin or mucosa. In some reports, titers of IgG4 antikeratinocyte antibodies correlated with disease activity. Dsg1 and 3 autoreactive CD4 + T-cells are detected in patients.

Current management/treatment

Treatment, especially in its severe form, is challenging. Historically, this disease was associated with a high morbidity and mortality. Introduction of corticosteroids reduced the mortality rate from 70-100% to 30%. However, long-term administration of high dose corticosteroids can be associated with severe adverse effects. Other therapeutic options include dapsone, gold, and systemic antibiotics, which are often used in combination with other immunosuppressant agents (azathioprine, methotrexate, cyclophosphamide). Other therapies, some experimental, used include mycophenolate mofetil, chlorambucil, cyclophosphamide, TPE, ECP, IVIG, rituximab, cholinergic receptor agonists, desmoglein 3 peptides and p38 mitogen-activated protein kinase inhibitor.

Rationale for therapeutic apheresis

The rationale for using TPE and IA in pemphigus vulgaris treatment is because there are circulating pathogenic autoantibodies. TPE has been utilized in patients with severe symptoms who either received high doses of conventional agents and/or had an aggressive and rapidly progressive disease or treatment resistant. TPE was used in patients in all age groups (13-80 years). The duration of disease prior to TPE use ranged 1 month to 25 years. The TPE goal was to reduce the level of autoantibodies and improve clinical symptoms. In one multicenter RCT patients were randomized into prednisolone alone (n = 18) and prednisolone plus 10 large volume TPE (n = 22) over four weeks (Guillaume, 1988). There were four septic deaths and no steroid sparring effect in TPE arm. IA has been promoted in Europe with increasing number of patients treated and reported clinical responses. Monocentric CRs and CSs showed in the adjuvant setting decrease of the circulating antibodies, which correlated to the improvement of bullous-erosive lesions, and corticoid sparing effect. Selective plasma exchange that uses a selective membrane plasma separator and DFPP have also been tried with some success.

Technical notes

TPE protocols vary widely in volume treated (400-4000 mL) and have been based on observed clinical response after each treatment. Though, more recent reports noted that 1 TPV is preferable in patients who are resistant to conventional therapy. Autoantibody levels rebounded within 1-2 weeks after TPE discontinuation, thus corticoids were used for continued immunosuppressive therapy. Clinical response with ECP was observed after 2-7 cycles (two daily procedures per month). Total number of cycles varied from 2-51. In one report 100% clinical response with decreased autoantibody titer was reported, follow-up 4-51 months. The disease was controlled in most patients; steroids could be tapered but rarely discontinued.

Volume treated: TPE: 1-1.5 TPV; ECP: Typically, MNCs are obtained from processing 1.5L of whole blood, but volume processed varies based on patient weight and HCT. 2-process method collects and treats MNCs obtained from processing 2 TBV; IA: 2-4 TBV

Frequency: TPE: Daily or every other day; IA: First week 3 daily, then weekly and tapering; ECP: Two consecutive days (one series) every 2 or 4 weeks

Replacement fluid: TPE: Albumin, plasma; ECP: NA; IA: NA

Duration and discontinuation/number of procedures

Approach should include monitoring of autoantibody titers and clinical symptoms. For TPE and IA, lack of clinical response after a trial period with concomitant adequate immunosuppression should be enough to discontinue treatment. For ECP, treatments were continued until clinical response was noted.

Keywords: pemphigus vulgaris, immunoadsorption, plasma exchange, extracorpeal photopheresis

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PERIPHERAL VASCULAR DISEASES

Prevalence: 3-10% of population (US)		**Procedure**	**Recommendation**	**Category**
		LA	Grade 1B	II
# reported patients: 100-300	**RCT**	**CT**	**CS**	**CR**
	1(42)	0	7(151)	NA

Description of the disease

Peripheral vascular disease (PVD) also known as peripheral arterial disease (PAD) or peripheral artery occlusive disease (PAOD) is a condition with narrowing and hardening of the arteries that supply the legs or arms. Pathophysiological factors involving PVD include atherosclerosis, endothelial cell dysfunction, and defective nitric oxide metabolite physiology. Atherosclerosis results in walls of the arteries being stiffer and unable to dilate and leads to insufficient blood flow. It is more common in men >50 years. Risk factors include smoking, diabetes mellitus, dyslipidemia, hypertension, coronary artery disease, renal disease on hemodialysis, and cerebrovascular disease. PVD is a strong risk factor for cardiovascular disease.

Clinical presentation of PVD may be asymptomatic or exhibit claudication (pain, achiness, fatigue, burning, or discomfort in the affected muscles triggered by walking or exercise and released by resting), pain and cramps at rest, ulcers or wounds that are slow to heal or do not heal, noticeable color or temperature change, diminished hair and nail growth on affected limb and digits, impotence, as well as other symptoms. Diagnosis of PVD is made through the ankle brachial pressure index (ABPI/ABI), followed by a lower limb Doppler ultrasound examination for site and extent of atherosclerosis. In addition, angiography, computerized tomography, and magnetic resonance imaging are also used.

PVD is commonly categorized with the Fontaine stages: stage 1) mild pain when walking (claudication), incomplete blood vessel obstruction; stage 2) severe pain when walking relatively short distances (intermittent claudication), pain triggered by walking "after a distance of >150 m in stage II-a and after <150 m in stage II-b"; stage 3) pain while resting (rest pain), mostly in the feet, increasing when the limb is raised; and stage 4: biological tissue loss (gangrene) and difficulty walking.

Current management/treatment

Management of PVD includes risk reduction, such as smoking cessation, optimal management of diabetes, hypertension, hypercholesterolemia, use of antiplatelet drugs and regular exercise. Cilostazol and pentoxifylline have been used to relieve symptoms of claudication. In severe cases, angioplasty and stent placement of the peripheral arteries or peripheral artery bypass surgery of the leg can be performed. In Japan, LA has been used routinely to treat PVD and has been approved for use in Fontaine’s stage 2 or higher when surgical therapy is unavailable, or conventional therapy is not effective.

Rationale for therapeutic apheresis

LA can decrease LDL cholesterol, the oxidized LDL, C-reactive protein (CRP), and fibrinogen transiently. One RCT in men with primary hypercholesterolemia and extensive coronary atherosclerosis, randomized patients to receive either biweekly LA plus simvastatin (n=21) or simvastatin (n=21) only (Kroon, 1996). The LA plus simvastatin arm showed decreases in levels of apolipoprotein B, total cholesterol, and lipoprotein(a) levels, decreased intima-media thickness of the carotid artery, and lack of an increase in the number of clinically significant stenoses in the lower limbs as compared to the control arm. A study in 28 patients with PVD treated with 10 sessions of LA (2 times per week for 5 weeks) with follow-up after 3 months, showed overall improvement including 82% in foot chillness or numbness, 54% in intermittent claudication, and 14% in foot ulcer (Kobayashi, 2005). Another study demonstrated improvement in physiological parameters such as ABI, maximum tolerated walking distance (MTWD) and clinical symptoms in 31 patients with PVD after an average of 9.6±0.8 sessions of LA (Tsuchida, 2006). One study showed a significant enhancement in tissue blood flow of both the head and lower limbs after LA treatment in 18 patients (Ebihara, 2007). Similarly, clinical improvement was observed in 10 out of 19 hemodialysis patients with PVD and treated with 10 sessions of LA (Tsurumi-Ikeya, 2010). In the patients who responded, LA resulted in a short-term decrease in total cholesterol and LDL cholesterol and a long-term reduction of the circulating levels of oxidized LDL, CRP, and fibrinogen. LA, in conjunction with below knee endovascular therapy (BK-EVT), resulted in lower major adverse limb event (amputation and re-intervention) rates compared to those who underwent BK-EVT alone (Ohtake, 2016).

Technical notes

Angiotensin converting enzyme (ACE) inhibitors are contraindicated in patients undergoing LA. The columns function as a surface for plasma kallikrein generation which, in turn, converts bradykininogen to bradykinin. Kininase II inactivation of bradykinin is prevented by ACE inhibition resulting in unopposed bradykinin effect, hypotension and flushing. This is not seen with the HELP system.

Volume treated: 3000-5000 mL of plasma	**Frequency:** Once or twice per week
Replacement fluid: NA	

Duration and discontinuation/number of procedures

Ten treatments in less than an 8-week period have been used.

Keywords: Peripheral vascular disease, peripheral artery occlusive disease, LDL apheresis

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PHYTANIC ACID STORAGE DISEASE (REFSUM'S DISEASE)

Incidence: Rare		**Procedure**	**Recommendation**	**Category**
		TPE/LA	Grade 2C	II
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
TPE	0	0	2(12)	12(13)
LA	0	0	2(8)	2(2)

Description of the disease

Phytanic acid storage disease (Refsum's Disease; now belongs to Zellweger spectrum disorders, part of peroxisomal disorders), also known as heredopathia atactica polyneuritiformis, is an autosomal recessive disorder first described by Sigvald Refsum, a Norwegian neurologist, in 1946. Patients have significant defects in the metabolism of phytanic acid (PA) due to deficiency or enzyme defect in phytanoyl-CoA hydrolase. This branched chain fatty acid is derived exogenously from dietary sources. The inability to degrade PA results in its accumulation in fatty tissues, liver, kidney, myelin, and in lipoproteins in the plasma. Clinical consequences are largely neurological including retinitis pigmentosa, peripheral neuropathy, cerebellar ataxia, sensorineural deafness, and anosmia. Other manifestations include skeletal abnormalities, cardiac arrhythmia, and ichthiosis. The clinical progression is typically slow and gradual with onset of signs and symptoms during the 2nd or 3rd decades of life due to the gradual accumulation of PA from dietary sources. The most frequent earliest clinical manifestations are night blindness and visual disturbances. Progression of symptoms can lead to retinitis pigmentosa, and possibly loss of sight. Patients with cardiac manifestation may experience arrhythmias, which could be fatal or prompt cardiac transplantation.

Current management/treatment

Limiting intake of PA by dietary restriction to 10 mg daily is the cornerstone of therapy. PA comes primarily from animal sources such as dairy, butter, cheeses, meats, and some fish. Diet alone can benefit many patients and lead to reversal of neuropathy and icthiosis. Care is taken to maintain overall general nutrition and caloric intake to avoid rapid weight loss, which can precipitate clinical relapse due to sudden mobilization of PA from liver and adipose tissue stores. The relative unpalatability of diets low in PA limits compliance with, and thus the effectiveness of, dietary management of this disorder. Even with adequate dietary compliance, there can be a delay in the fall of PA levels presumably because of its release from adipose tissue stores.

Rationale for therapeutic apheresis

TPE rapidly reduces plasma PA in the setting of acute attacks or exacerbation of the disease as well as for maintenance therapy. The normal plasma PA level in humans is <33 mmol/L. Symptomatic levels of PA in Refsum Disease range from 700-8,000 mmol/L. Several small CS and isolated CRs have described clinical improvements in patient signs and symptoms with TPE in conjunction with dietary control. TPE has been found to improve polyneuropathy, ichthiosis, ataxia, and cardiac dysfunction in most but not all patients treated. Unfortunately, as is also reported with dietary treatment alone, visual, olfactory, and hearing deficits do not respond. Patients may experience severe exacerbations of disease during episodes of illness or weight loss, such as during the initiation of dietary management. PA levels increase dramatically, possibly due to mobilization of PA stored in adipose tissue. CRs and CS have used TPE to treat episodes with marked rapid improvement in symptoms. Chronic TPE strategies have been described which attempt to deplete PA stores following initiation of dietary therapy or to allow for less restrictive diets. Since PA is also bound to plasma lipoproteins and triglycerides, successful management of PA levels with LA using double-membrane filtration or dextran sulfate plasma perfusion LA has been reported in two CRs and two CS totaling 8 patients (Straube, 2003, Zolotov, 2012). In LA, the efficiency of PA removal was found to be equivalent to TPE but with less IgG loss. In one CS, patients were treated for as long as 13 years with weekly to biweekly LA resulting in lowering of PA levels, improvement in nerve conduction studies, and stabilization of vision (Zolotov, 2012).

Technical notes

Although approaches to therapeutic apheresis for Refsum's Disease vary, a typical course consists of 1-2 TPE per week for several weeks to a month. In some cases, maintenance TPE continues with decreasing frequency over subsequent weeks to months. When LA has been used for chronic therapy, treatments have been weekly to every other weekly.

Volume treated: TPE: 1-1.5 TPV; LA: 3 L	**Frequency:** Daily for acute exacerbation; variable for chronic therapy
Replacement fluid: TPE: albumin; LA: NA	

Duration and discontinuation/number of procedures

Therapeutic strategy is ultimately determined by monitoring the patient's PA level, clinical signs, and symptoms, and the need to control or prevent exacerbations of the disease. If chronic therapy is initiated, procedures should be performed lifelong.

Keywords: Phytanic acid storage disease, Refsum disease, heredopathia atactica polyneuritiformis, plasma exchange, selective removal, LDL apheresis

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POLYCYTHEMIA VERA; ERYTHROCYTOSIS

Incidence: PV: 1/100,000/yr	**Indication**	**Procedure**	**Recommendation**	**Category**
	Polycythemia vera	Erythrocytapheresis	Grade 1B	I
	Secondary erythrocytosis	Erythrocytapheresis	Grade 1C	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Polycythemia vera	0	3(225)	6(612)	NA
Secondary erythrocytosis	0	0	6(307)	NA

PV = polycythemia vera

Description of the disease

Absolute erythrocytosis is defined as an RBC mass of at least 25% above the age and gender-specific mean predicted value. Hematocrit (HCT) values >60% for adult males and >56% for adult females, is indicative of absolute erythrocytosis, as these levels cannot be achieved with plasma volume contraction alone or other causes. Primary erythrocytosis refers to the myeloproliferative disease, polycythemia vera (PV), in which an abnormal hematopoietic stem cell clone autonomously overproduces RBCs. Additional features of PV include splenomegaly, granulocytosis, thrombocytosis and mutations of the tyrosine kinase JAK2 (>90% of cases), as well as the tumor suppressor *TET2* mutation (up to 22%). Secondary erythrocytosis refers to isolated RBC overproduction due to a congenital erythropoietic or hemoglobin defect, chronic hypoxia related to a respiratory or cardiac disorder, ectopic endogenous erythropoietin production, therapeutic erythropoietin administration, or without a primary disorder or features of PV (i.e., idiopathic erythrocytosis).

Whole blood viscosity increases significantly as the HCT level exceeds 50%. Symptoms of hyperviscosity include headache, dizziness, slow mentation, confusion, fatigue, myalgia, angina, dyspnea and thrombosis. Altered blood flow rheology increases the risk of thrombosis by pushing the platelets closer to the vessel edge, increasing vessel wall and von Willebrand factor interaction. Altered antifibrinolytic activity, clot resistance to fibrinolysis, endothelial dysfunction and platelet function may account for the increased thrombotic risk, which is encountered in 15-40% of PV patients. Uncontrolled erythrocytosis (HCT >55%), age >60 years, and history of prior thrombosis are considered high risk for thrombotic complications. The risk of transformation to myelofibrosis or acute myeloid leukemia is 3 and 10% 10-year risk, respectively.

Current management/treatment

Management of low risk PV includes phlebotomy, with the goal to maintain the HCT ≤ 45% and low dose aspirin. Phlebotomy results in iron deficiency, which decreases RBC overproduction. PV associated with extreme thrombocytosis (platelet count >1,000x10^9/L) may be associated with increased bleeding risk due to acquired von Willebrand syndrome. High risk PV patients are treated with phlebotomy, aspirin and cytoreductive agents, such as hydroxyurea. The FDA has approved a JAK inhibitor, ruxolitinib, for use in patients with inadequate response or intolerance to hydroxyurea. Other treatments such as busulfan and IFN-α may also be considered as second-line therapy for those patients in whom hydroxyurea is ineffective or poorly tolerated. In secondary erythrocytosis, treatment of the underlying cause is preferred; long-term supplemental oxygen and/or continuous positive airway pressure maneuvers for hypoxia; surgical interventions for cardiopulmonary shunts, renal hypoxia or an Epo-producing tumor; ACE-I and A2R for post-renal transplantation erythrocytosis. When an underlying disorder cannot be reversed, symptomatic hyperviscosity can be treated by isovolemic phlebotomy.

Rationale for therapeutic apheresis

Erythrocytapheresis, like isovolemic phlebotomy, corrects hyperviscosity by lowering the HCT, which reduces capillary shear, increases microcirculatory blood flow and improves tissue perfusion. The target HCT appears to be the most important risk factor for undesirable outcomes. An RCT of 365 patients with PV found that patients kept at a target HCT < 45% compared to HCT 45-50% had significantly lower rate of cardiovascular death and major thrombosis (Marchioli, 2013). Erythrocytapheresis reduces the HCT more efficiently than simple manual phlebotomy and can increase interprocedural time and decrease the number of procedures needed to achieve the target HCT. The decision to use an automated procedure over simple phlebotomy should include consideration of the risks. For severe microvascular complications or significant bleeding manifestations, erythrocytapheresis may be a useful alternative to large-volume phlebotomy; particularly if the patient is hemodynamically unstable. Erythrocytapheresis prior to surgery can be used to reduce the high risk of perioperative thrombotic complications if HCT >55%. A study of 76 PV patients found platelet function improvement after erythrocytapheresis, as measured by TEG, suggesting that the hemodilution achieved with the procedure may reduce thrombotic risk (Rusak, 2012). Thrombocytapheresis, as well as erythrocytapheresis, may be indicated for patients with PV with an acute thrombohemorrhagic event associated with uncontrolled thrombocytosis and erythrocytosis.

Technical notes

Automated instruments allow the operator to choose a post-procedure target HCT level and calculate the volume of blood removal necessary to attain the goal. One study found that using exchange volume < 15mL/kg and inlet velocity <45 mL/min, especially for patients >50 years may decrease adverse events (Bai, 2012); a proposed mathematical model for choosing most appropriate therapy parameters is available (Evers, 2014). During the procedure, saline boluses may be required to reduce blood viscosity in the circuit and avoid pressure alarms.

Volume treated: Volume of blood processed is based on TBV, starting HCT and desired post-procedure HCT

Frequency: As needed for symptomatic relief or to reach desired HCT (usually one)

Replacement fluid: Albumin, normal saline

Duration and discontinuation/number of procedures

In patients with PV, the goal is normalization of the HCT (<45%). For secondary erythrocytosis, the goal is to relieve symptoms but retain a residual RBC mass that is optimal for tissue perfusion and oxygen delivery. A single procedure should be designed to achieve the desired post-procedure HCT.

Keywords: Erythrocytosis, polycythemia vera, erythrocytapheresis, blood hyperviscosity, phlebotomy, myeloproliferative disorder, myeloproliferative neoplasm

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POST-TRANSFUSION PURPURA (PTP)

Incidence: 2/100,000 transfusions		**Procedure**	**Recommendation**	**Category**
		TPE	Grade 2C	III
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	1(3)	15(23)

Description of the disease

Post-transfusion purpura (PTP) is a rare and delayed transfusion-related complication characterized by severe and abrupt onset of profound thrombocytopenia (platelet count $<10 \times 10^9$/L) 5-10 days after transfusion of any platelet-containing blood component. It is more commonly seen in women following RBC transfusion and can present with widespread purpura, bleeding from mucous membranes, and in severe cases intracranial hemorrhage and death. PTP occurs most frequently in patients whose platelets lack the HPA-1a platelet antigen and who have previously developed alloantibodies against HPA-1a due to immunization during pregnancy or blood transfusion. Other platelet alloantibodies have also been implicated. Clinical entities that should be excluded from the differential diagnosis include drug-induced thrombocytopenia (including heparin-induced thrombocytopenia (HIT)), immune thrombocytopenia (ITP), sepsis, and disseminated intravascular coagulopathy (DIC). The diagnosis may be confirmed by the presence of platelet specific alloantibodies. The pathogenesis of PTP remains incompletely understood; what is apparent is presence of destruction of both transfused and autologous platelets. There are currently four hypotheses to explain the destruction of autologous antigen negative platelets observed in patients with PTP: 1) immune complex mediated platelet destruction via binding of the Fc receptor leading to platelet clearance; 2) soluble platelet antigens, possibly derived from platelet microparticles, passively transferred in the blood product which bind to the patient's platelets and provide a target for the alloantibody; 3) an alloantibody that also exhibits auto reactivity; and 4) an autoantibody which develops in conjunction with the alloantibody. The detection of alloantibodies (generally high titer) against HPA-1a, or other platelet antigens, supports the PTP diagnosis. These high titer antibodies can be detected for up to one year after the PTP episode. PTP is generally self-limited, with complete recovery in about 20 days, even in untreated patients. The mortality associated with PTP can be up to 5-10% due to fatal hemorrhage. PTP recurrence after future transfusion is uncommon.

Current management/treatment

The current treatment for PTP is administration of high dose IVIG (2/kg/day over 2-5 days), resulting in a 90% response rate. IVIG may act by blocking the Fc receptor of the reticuloendothelial system. All nonessential transfusions of blood components should be immediately discontinued. A bleeding patient should be transfused with alloantigen negative platelets, if available. Alloantigen positive platelet transfusion is generally ineffective and may stimulate more antibody production. However, if the patient is actively bleeding, platelet transfusion may decrease bleeding tendencies. High doses of corticosteroids are used but appear not to change the disease course. There is a single CR of response to splenectomy in a patient who was not responsive to IVIG, steroids, or TPE (Cunningham, 1989).

Rationale for therapeutic apheresis

Removal of platelet alloantibodies by TPE decreases the antibody titer and may remove residual soluble alloantigen; thereby increasing platelet survival and reversing the bleeding risk. Based on the limited CRs, TPE seems to shorten the duration of thrombocytopenia. If IVIG is not effective, TPE may be considered when hemorrhage is present.

Technical notes

Due to severe thrombocytopenia, the anticoagulant ratio should be adjusted accordingly. ACD-A may be preferred for anticoagulation due to increased bleeding risk associated with heparin in the setting of profound thrombocytopenia. Typically, the replacement fluid is albumin to avoid further exposure to HPA-1a antigen that may still be present in plasma. However, in bleeding patients, plasma may be given towards the end of procedure to maintain clotting factor levels.

Volume treated: 1-1.5 TPV	**Frequency:** Daily
Replacement fluid: Albumin, plasma	

Duration and discontinuation/number of procedures

TPE can be discontinued when platelet count starts increasing ($>20 \times 10^9$/L) and clinically significant bleeding improves.

Keywords: Post transfusion purpura, plasma exchange, intravenous immunoglobulin, HPA-1 antigen, platelet antibody

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PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) ASSOCIATED WITH NATALIZUMAB

Incidence: 4/1000		**Procedure**	**Recommendation**	**Category**
		TPE	Grade 1C	III
# reported patients: 100-300	**RCT**	**CT**	**CS**	**CR**
	0	0	6(276)	NA

Description of the disease

Progressive multifocal leukoenchephalopathy (PML) is a rare CNS demyelinating disorder typically seen in patients with impaired cell-immunity. The pathogenesis involves reactivation of latent polyoma JC virus (JCV) from peripheral reservoirs invade the CNS, leading to necrosis of oligodendrocytes and myelin sheath disresolution. Clinical manifestations are highly variable, generally gradually progressive, and commonly include motor, language, cognitive, and visual impairment. They do not involve the optic nerve or spinal cord in contradistinction to the deficits associated with MS relapse. Demonstration of JCV DNA by ultrasensitive PCR in the CSF with characteristic radiographic findings in appropriate clinical setting is diagnostic for PML.

Natalizumab, which is approved as a monotherapy for relapsing forms of MS, is a humanized monoclonal antibody against the α4-subunit of α4β1 and α4β7 cellular adhesion integrins; thus, inhibiting adhesion and migration of lymphocytes into tissues. Thus, lymphocytes transmigration into CNS parenchyma via the blood brain barrier is reduced, leading to decreased inflammation.

Natalizumab-associated PML (NTZ-PML) arises in a complex fashion. The compromised brain immune surveillance by blockage of lymphocyte transmigration is important. Mobilization of JCV carrying cells from the bone marrow and altered expression of transcriptional factors at the cellular level important for viral tropism are also likely contributory. Risk factors for increased incidence include JCV antibody seropositivity, prior immunosuppressive therapy, and longer duration of treatment (>2 years). PML was also described, although much less frequently, with other monoclonal antibodies (alemtuzumab, rituximab).

Current management/treatment

Prevention of PML development with risk stratification approaches are warranted. Immune reconstitution is the only intervention with demonstrated efficacy for PML. For NTZ-PML, management includes discontinuation of the drug (temporary or permanent) and consideration for initiation of TPE to accelerate clearance, especially if the drug is recently infused. Both will increase number and function of leukocytes migration to the CNS.

Rapid immune reconstitution may precipitate an extreme immune response called Immune Reconstitution Inflammatory Syndrome (IRIS), which associated with neurological status deterioration, often life threatening. IRIS usually develops 2-6 weeks after TPE (versus 3 months after drug discontinuation) in almost all patients. In NTZ-PML, IRIS stems from massive influx of lymphocytes into the CNS following the antibody's clearance leading to renewed immune surveillance and increased inflammation. Abrupt worsening of neurologic symptoms in patients treated with TPE therefore most likely represent IRIS and not worsening disease course. The recommended treatment of IRIS is high-dose corticosteroids and not TPE. Given the possible involvement of chemokine receptor 5-postive (CCR5+) T cells in IRIS pathophysiology, a CR described the successful use of maraviroc, a CCR5 antagonist, in IRIS prevention in post-TPE NTZ-PML (Giacomini, 2014). However, there have been no RCTs of either therapeutic intervention.

Rationale for therapeutic apheresis

Natalizumab's long duration of action delays immune reconstitution for several months. Unrestrained PML is often lethal in the 3 months after symptoms start and thus reversal of ongoing JC infection is crucial. Although the pharmacokinetic half-life in MS patients is ~11 ± 4 days, natalizumab is detectable up to 200 days in the circulation after cessation of therapy. It also has been shown that mean α4-integrin saturation levels remain >70% at 4 weeks after infusion. One study showed that serum natalizumab levels 1-week post TPE were reduced by an average of 92% from baseline with 75 ± 28% reduction 4 weeks after natalizumab infusion when comparing same patients with and without TPE (Khatri, 2009). Additionally, desaturation of the α4-integrin receptor to <50% was achieved when natalizumab concentration was <1μg/mL (therapeutic level). Lastly, TPE significantly increased leukocyte transmigration ability in vitro. Thus, TPE accelerates removal of natalizumab, decreases receptor saturation, and restores leukocyte transmigration. The net result is to allow lymphocytes to adhere to vascular endothelium and rapidly restore immune function which may improve clinical outcomes. However, one retrospective study of 219 NTZ-PML patients did not find an association between TPE and mortality and residual disability; however, it lacks statistical power to conclusively exclude the benefit of TPE (Landi, 2017). Furthermore, in a study of 42 patients, the duration of IRIS was longer in TPE patients and thus, it cautioned against TPE usage; however, TPE was not associated with IRIS latency (Scarpazza, 2017). Nonetheless, these retrospective studies had major limitations including containing small number of patients and potential differences in baseline characteristics between the groups received TPE and the group did not. Thus, the benefits of immune reconstitution in patients with severe NTZ-PML may outweigh the risk of IRIS and although the role of TPE is not yet optimized in this condition and that the benefits of TPE are conjectural, and have not been proven rigorously, it can be considered in selected group of patients.

Technical notes

The benefit of TPE in controlling the JC viral infection is counterbalanced by the potential of more severe and longer IRIS. It may not accelerate normalization of some key biological effect of natalizumab better than stopping the drug. Some authors have superficially described the use of IA with TPE as possible alternative for TPE but no detailed experience of using it alone has been described.

Volume treated: 1-1.5 TPV	**Frequency:** Every other day
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

5 TPE procedures (most commonly used in reported cases) is needed for >95% of patients to lower natalizumab levels <1 μg/mL, which may be used as a post-TPE target (Khatri, 2009).

Keywords: Natalizumab, progressive multifocal leukoencephalopathy, multiple sclerosis, immune reconstitution inflammatory syndrome, plamsa exchange

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PRURITUS DUE TO HEPATOBILIARY DISEASES

Incidence: Rare	**Indication**	**Procedure**	**Recommendation**	**Category**
	Treatment resistant	TPE	Grade 1C	III
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	3(10)	8(10)

Description of the disease

Chronic pruritus can present in patients with a variety of hepatobiliary disorders including primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), cholangiocarcinoma, inherited cholestasis, and intrahepatic cholestasis of pregnancy. Cholestasis may be caused by hepatocellular secretory failure, bile duct damage, or obstruction of the bile duct system. Up to 70-80% of patients with PBC and PSC may experience pruritus, while pruritus is less frequently seen in patients with obstructive cholestasis.

Pruritus may range from mild and tolerable to difficult and intolerable, limiting daily life activities, causing severe sleep deprivation, depression, and even suicidal ideation. Pruritus tends to intensify during the evening, limbs and, in particular, palms and soles have more severe pruritus, but it can be generalized. However, no primary causing skin lesions are identified. For females, pruritus is affected by hormones and is worse during the progesterone phase of the menstrual cycle, pregnancy, and hormone replacement therapy.

The pathogenesis of pruritus in cholestasis remains to be defined. Previously bile salts, endogenous μ-opioids, histamine, serotonin, and steroids were thought to be causative agents, but no firm correlation has been established. Recent studies have demonstrated that neuronal activator lysophosphatidic acid and autotaxin (an enzyme forming lysophosphatidic acid) correlate to the severity of pruritus and the treatment efficacy.

Current management/treatment

Medication therapy includes: 1) first-line: anion exchange resin cholestyramine to remove the pruritogen(s) from the enterohepatic cycle in mild pruritus, 2) second-line: rifampicin to modulate central itch and/or pain signaling, 3) third-line: naltrexone (μ-opioid antagonist, modulate central itch and/or pain signaling), and 4) fourth-line: sertraline (modulate central itch and/or pain signaling). For patients unresponsive to medications, other measures may be used: 1) nasobiliary and transcutaneous drainage or external biliary diversion to remove the pruritogen(s) from the enterohepatic cycle, 2) anion absorption, TPE or extracorporeal albumin dialysis to remove the potential pruritogen(s) from the systemic circulation, and 3) liver transplantation.

Rationale for therapeutic apheresis

TPE may remove the potential pruritogen(s) from the systemic circulation. Out of 13 reported cases of patients with chronic pruritus due to hepatobiliary disorders, 10 (77%) responded to TPE. Patient may experience decreased pruritus after the second TPE. For some patients, the effect may last many months, while for others, chronic maintenance TPE is needed.

Technical notes

Volume treated: 1-1.5 TPV	**Frequency:** 3 (weekly or biweekly) procedures initially, then 2-4 times per month for maintenance
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

Some may require long term TPE, treatment is individualized based on patient's symptoms.

Keywords: pruritus, plasma exchange, primary biliary cirrhosis, primary sclerosing cholangitis

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PSORIASIS

Incidence: 60-100/100,000; Caucasian > African-Americans	**Indication**	**Procedure**	**Recommendation**	**Category**
	Disseminated pustular	ECP	Grade 2B	III
		Adsorptive cytapheresis	Grade 2C	III
		TPE	Grade 2C	IV
# reported patients: 100-300	**RCT**	**CT**	**CS**	**CR**
ECP	0	0	2(12)	0
Adsorptive cytapheresis	0	1(44)	5(45)	9(12)
TPE	0	1(6)	3(23)	0

Description of the disease

Psoriasis is a chronic immune-mediated, skin disorder with high genetic predisposition. Plaques and papules are the result of hyperproliferation and abnormal differentiation of epidermis which leads to its thickening (acanthosis). Inflammatory infiltrate consisting of dendritic cells, macrophages, neutrophils and T cells in the dermis with some T cells in the epidermis, contribute to overall thickness of lesions. The disease process involves upregulation of Th1 and Th17 pathways with T cell transport from the dermis into epidermis as key event. Recirculation of T cells in the skin leads to keratinocyte proliferation. Imbalance is further affected by a decrease in activity but not number of T regs and decreased levels of IL-10. Complex feedback loops between the innate and adaptive immune system mediated by cytokines plays an instrumental role in the development of the pathological changes seen in psoriasis. Psoriatic T cells predominantly secrete interferon-γ and interleukin-17 while activated dendritic cells produce TNF-α and intelukin-23.

Clinical types of psoriasis are plaque (psoriasis vulgaris), guttate, pustular, inverse, nail and erythrodermic. Except for widespread pustular or erythrodermic psoriasis the disease rarely causes death, though with high prevalence hundreds of deaths are reported annually. Inheritance of psoriasis is complex, with at least 9 chromosomal loci called psoriasis susceptibility (PSORS) being involved (e.g., *PSORS1* is located within MHC region on chromosome 6p21). Some clinical presentations are strongly associated with PSORS (e.g., guttate psoriasis with *PSORS1*). Generalized pustular psoriasis is often present in patients with existing or previous psoriasis vulgaris but can also develop in people without a history of psoriasis. In these patients the cause is often identified as a deficiency of interleukin-36 receptor antagonist (DITRA), due to mutation of *IL36RN*.

Psoriatic arthritis, an inflammatory arthropathy can occur in 10-30% of patients with psoriasis. Arthritis develops before psoriasis in up to 15% of those with psoriatic arthritis. Many genetic associations have been identified with psoriatic arthritis including HLA-B27.

Current management/treatment

Topical and systemic therapies are available. Therapy is generally dictated by disease severity, comorbidities, patient's preferences and adherence to treatment. Moderate to severe psoriasis is defined as 5-10% involvement of body surface area. Topical therapies include emollients, corticosteroids, topical vitamin D analogs (calcipotriene, calcitriol), topical retinoids, topical calcineurin inhibitors (tacrolimus, pimecrolimus) and tar. Different modalities of ultraviolet light are used and include phototherapy (UVB light +/- tar), narrow band UVB, photochemotherapy (PUVA, oral or bath psoralen followed by UVA radiation) and excimer laser. Systemic therapies include methotrexate, retinoids, systemic immunosuppression (cyclosporine). In the past decade several biologics have been approved for psoriasis and are being used more frequently. TNF-alpha inhibitors (etanercept, infliximab and adalimumab) and ustekinumab, a human monoclonal antibody against IL-12 and IL-23, are approved for treatment of moderate - severe psoriasis. Secukinumab has been approved as the first monoclonal antibody blocking IL-17A, a key effector cytokine produced by TH17 and other cells. Clinical response is often evaluated using Psoriasis Area and Severity Index (PASI score; 0-72) which evaluates 3 features of psoriatic plaque (redness, scaling and thickness) and extent of involvement of each body area.

Rationale for therapeutic apheresis

Few small studies showed that TPE, including cascade filtration, provides no benefit in the treatment of psoriasis. The rationale for these studies was removal of cytokines and putative "psoriatic factor", which at that time were considered contributory to the disease process; however, this is not consistent with current understanding. Granulocyte and monocyte adsorption apheresis (GMA) remove activated granulocytes and monocytes using a column packed with cellulose acetate beads. The selective removal of leukocytes through the column provides for a reasonable pathophysiological justification especially in context of disseminated pustular psoriasis. In one study 15 patients received 5 treatments (1/wk) in addition to standard therapy. There was 86% response rate, though the contribution of apheresis is difficult to discern as other therapies were used concurrently (Ikeda, 2013). Several smaller studies confirmed improvement in clinical symptoms. In a study of 20 patients with refractory psoriatic arthritis, 65% of patients demonstrated a 20% improvement in joint symptoms and signs following 5-10 GMA sessions. This response was maintained in at least 28% of patients for over 20 weeks (Kanekura, 2017). The use of lymphocytapheresis using MNC has been described in several earlier small studies. Lymphocytapheresis was performed by an automated centrifuge-based continuous-flow blood cell separator. The rationale for its use is similar to described above. The reported response rate was similar to that shown with adsorptive granulocyte-monocyte columns. However, apheresis treatment could be only considered in highly selected group of patients with disseminated disease and lack of response to other systemic treatments.

Better understanding of pathophysiology of psoriasis suggests that ECP might be used in its treatment. Several studies have shown a variable response (Adamski, 2015).

Technical notes

Granulocyte-monocyte adsorptive columns are not available in the US.

Volume treated: Adsorption: 1,500-2,000mL; ECP: process 1.5L of whole blood (volume varies based on patient weight and HCT); 2 step method (off-line)- process 2× TBV	**Frequency:** Adsorption: 1/week; ECP: One cycle/week for 4 months and then taper
Replacement fluid: NA	

Duration and discontinuation/number of procedures

Adsorptive columns are generally used for 5 weeks (total 5 treatments). ECP has been used for different lengths of time (2-12 weeks), adjusted based on the patient's presentation as well as the objective of the treatment.

Keywords: psoriasis, cascade filtration, lymphocytapheresis, extracorpeal photopheresis, plasma exchange, adsorptive cytapheresis

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RED CELL ALLOIMMUNIZATION, PREVENTION AND TREATMENT

Incidence: 15% of population is RhD negative; Pregnancy: 35/10,000 live births/yr (US)	Indication	Procedure	Recommendation	Category
	Exposure to RhD + RBCs	RBC exchange	Grade 2C	III
	Pregnancy, GA <20 wks	TPE	Grade 2C	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Exposure to RhD + RBCs	0	0	0	6(8)
Pregnancy, GA <20 wks	0	0	14(312)	29(33)

GA = gestational age; TPE is performed prior to intrauterine transfusion availability, not typically performed until GA is ≥20 weeks

Description of the disease

RBC alloimmunization is a complication of RBC transfusion. Patients with RBC alloantibodies are at risk for hemolytic transfusion reactions, and difficulty finding compatible RBC units. For females, alloimmunization can also cause hemolytic disease of the fetus and newborn (HDFN). Patients are transfused ABO and RhD compatible RBCs to prevent RhD alloimmunization. In life threatening bleeding, or low inventory, protocols are in place to provide rapid RBCs without the patient's blood type. Because of the limited availability of RhD negative (RhD-) RBC units (only 15% of Caucasians and 8% of African Americans are RhD-), these protocols involve the selection of Group O, RhD positive (RhD+) RBCs for males and older females (typically >50 years) to preserve RhD- RBCs units for females of childbearing potential. To mitigate the risk of anti-D formation in females of childbearing potential who received RhD + RBCs, several strategies have been attempted, including RBC exchange and/or Rh immunoglobulin (RhIg).

In HDFN, maternal IgG crosses the placenta causing hemolysis of fetal RBCs, leading to fetal anemia and when severe, hydrops fetalis and death. Traditionally severe HDFN is secondary to anti-D, but it can be caused by other alloantibodies (e.g., anti-K, -C/c, -E, -PP1Pk, and M). HDFN from anti-D and anti-Kell can have severe courses. RBC alloimmunization occurs after fetomaternal hemorrhage or transfusion. HDFN severity increases with subsequent pregnancies. Prophylactic RhIg during pregnancy and post-partum has reduced HDFN secondary to anti-D.

Current management/treatment

RBC exchange reduces volume of RhD+ RBCs allowing for safe RhIg administration. Studies have found the rate of RhD alloimmunization in RhD- recipients following RhD + RBC transfusions is 10-30% particularly in ill patients (Meyer, 2015). This rate is lower than the historical rate of 80%, which was determined in healthy prisoners. Proceeding with therapy to prevent RhD alloimmunization should be based on the risks of therapies balanced with the risk of RhD alloimmunization and potential for HDFN.

Reports described prevention of RhD sensitization following RhD + RBC transfusion to RhD- females. Reports calculated RBC transfusion volume and used RHIG following to prevent alloimmunization. Based on data from routine RhIg use in pregnancy, treatment should be within 72 hours of RhD + RBC exposure. RhIg dose and route (IV/IM) provided to patients varied; 18 μg/mL RhD + RBCs appears appropriate, although there is no specific guidance. Because of large RhIg doses, authors spaced doses out in 8-hour intervals; some used normal saline to support through potential hemolysis though most did not experience hemolysis.

The following describes management of a pregnant woman with a newly identified clinically significant RBC alloantibody: (1) history is obtained to identify exposure source (e.g., previous pregnancy or transfusion), (2) presumed father's RBCs are typed to assess for risk of inheritance. If the father does not express the antigen, no further work up is needed. If father's RBCs express the antigen, further testing determines whether the father carries 1 or 2 gene copies. (3) Sensitized pregnancies are monitored by middle cerebral artery (MCA) Doppler ultrasound (US) with velocimetry to detect fetal anemia along with RBC antibody titer. Critical titer thresholds are typically 8-32 though titer does not always correlate with risk/severity of HDFN (e.g., anti-Kell). (4) If the titer is above a critical threshold or increased by 2 dilutions, serial US should be performed. Institutions use US with velocimetry at 18 weeks gestational age (GA) to determine treatment rather than titer. Moderate-severe anemia is predicted when MCA measurement is >1.5 multiples of the median (MoM). (5) After this, cordocentesis assesses fetal hematocrit (HCT); if HCT <30%, intrauterine transfusion (IUT) is indicated. IUT cannot be technically or safely performed until ~20 weeks GA. (6) Amniocentesis for fetal lung maturity assessment determines whether the fetus can be safely delivered. (7) HDFN can cause neonatal hyperbilirubinemia, which can result in kernicterus so the neonate must be monitored.

Rationale for therapeutic apheresis

The goal of RBC exchange is to reduce circulating RhD+ RBCs to level at which RhIg can be safely administered. When the quantity of RhD+ RBCs is larger (usually ≥20% of circulating RBC volume), RBC exchange should be considered. Reports have described using RBC exchange at lower levels of RhD+ RBCs. All reports whether using exchange/RhIg or RhIg included follow-up (weeks to 1 year) without evidence of anti-D formation.

TPE may decrease maternal antibody titer and amount of antibody transferred to fetus, decreasing RBC destruction improving HDFN. The current mainstay of treatment is IUT, but if there is a high risk of fetal demise or signs of hydrops at <20 weeks GA, especially in a mother with a previously affected pregnancy, then TPE and/or IVIG may be indicated. Survival in severe cases with the use of TPE and/or IVIG prior to IUT is ~75%. Most patients also received IVIG and IUT. One CS highlighted the use of IA for severe Rh HDFN unresponsive to TPE and IVIG (Colpo, 2017). Another reported on the rebound effect TPE may have in alloantibody production (Barclay, 1980). TPE has not been shown to prevent future fetal anemia and subsequent IUT.

Technical notes

For RBC exchange, target fraction of RBCs remaining should be tailored to the volume of RhD+ RBCs received to achieve a volume that can be safely treated with RhIg. Authors varied on how much to exchange, 1 RCV was typical. Reports varied on maternal TPV to exchange for HDFN, 1 was average.

Volume treated: RBC exchange: 1-2 RCV; TPE: 1-1.5 TPV	**Frequency:** 1-3/week
Replacement fluid: RBC exchange: RhD- RBC units; TPE: Albumin	

Duration and discontinuation/number of procedures

One procedure should decrease circulating Rhd+ RBCs to a level that can be treated with RhIg.

TPE should be considered early in pregnancy (7-20 weeks) and continued until IUT can safely be administered (~20 weeks GA). Close monitoring of the fetus for signs of hydrops aids in guiding treatment.

Keywords: Hemolytic disease of the fetus and newborn, red cell alloimmunization, IUT, hydrops, plasma exchange, IVIG, Rh immunoglobulin, red cell exchange, RhD, Rh+

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SCLERODERMA (SYSTEMIC SCLEROSIS)

Incidence: 9-19/1,000,000/yr; 9:1 (F:M)		**Procedure**	**Recommendation**	**Category**
		TPE	Grade 2C	III
		ECP	Grade 2A	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
TPE	1(15)	7(132)	15(205)	NA
ECP	3(162)	0	5(87)	NA

Description of the disease

Systemic sclerosis (SSc) is a connective tissue disease characterized by the accumulation of collagen and other extracellular matrix proteins in skin, blood vessels, heart, lungs, kidneys, gastrointestinal (GI) tract, musculoskeletal and other organs, in particular with prominent skin fibrosis and associated Raynaud's phenomenon. There are two forms of SSc: diffuse cutaneous systemic sclerosis (dcSSc) and limited cutaneous systemic sclerosis (lcSSc). lcSSc presents with features of CREST (Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia), and typically with slower disease progression, but with increasing disability and disfigurement over time. dcSSc is characterized by thickening of the skin (scleroderma) and progressive visceral organ dysfunction due to fibrosis, and typically with rapid onset and decreased survival. Antinuclear antibodies are present in more than 95% of patients with SSc.

Current management/treatment

Routine management of SSc include systemic treatment such as hydroxychloroquine, methotrexate, mycophenolate mofetil and cyclophosphamide, and symptom relief. The 2016 European League Against Rheumatism (EULAR) recommendations include the following: a) SSc-Raynaud's phenomenon: dihydropyridine-type calcium antagonists, intravenous iloprost, and fluoxetine; b) digital ulcers in SSc: intravenous iloprost, PDE-5 (phosphodiesterase type 5) inhibitors; bosentan, especially after treatment failure with calcium channel blockers, PDE-5 inhibitors or iloprost therapy; c) SSc-PAH (pulmonary arterial hypertension): endothelin receptor antagonists, PDE-5 inhibitors or riociguat; intravenous epoprostenol for severe SSc-PAH; and prostacyclin analogues; d) SSc skin and lung disease: methotrexate for skin manifestations of early diffuse SSc; cyclophosphamide, in particular for SSc with progressive interstitial lung disease; and haematopoietic stem cell transplantation for rapidly progressive SSc at risk of organ failure; e) SSc renal crisis: ACE inhibitors; and glucocorticoids with risk justification and careful monitoring; f) SSc-related gastrointestinal disease: proton pump inhibitor, prokinetic drugs and intermittent or rotating antibiotics. Other treatments such as mesenchymal stem cell therapy, asiliximab, alemtuzumab, and abatacept have also been studied.

Rationale for therapeutic apheresis

TPE has been used for SSc with the rational that humoral factors might play an important role in the pathogenesis. Long-term TPE (2-3 weekly for 2 weeks, 1 TPE weekly for 3 months, and 1 TPE every other week as a maintenance therapy) was evaluated in a CT. All serological markers improved in comparison to the control group; however, there was no difference in clinical outcomes (Cozzi, 2001). In a CS reporting on 15 patients who received TPE in combination with prednisone and cyclophosphamide, 14 patients had clinical improvement (Dau, 1981). In a CS of scleroderma renal crisis, adding TPE to ACE inhibitors in patients who developed microangiopathy or were intolerant to high dose of ACE inhibitors showed preservation of renal function enough to avoid dialysis as well as improved 5-year survival rates (Cozzi, 2012). A comprehensive review analyzed 572 patients reported in the literature (including abstracts and non-English publications), of which 455 received TPE. They reported that most patients receiving TPE had improvements, in particular in Raynaud's symptoms and digital ulceration after just 3-4 weekly treatments (Harris, 2018).

ECP (2 treatments every month) was used in the treatment of scleroderma in a sham RCT of 64 patients. The study was statistically underpowered to reveal significant differences between the two study arms. However, serial measurements within each group showed significant improvements in skin scores and mean joint involvement after 6 and 12 months in the ECP group but not in the sham group (Knobler, 2006). An earlier multicenter RCT of 79 patients with recent onset disease also showed a statistically significant improvement in skin and joint parameters at 6 months among 68% of ECP treated patients compared to 32% on D-penicillamine (Rook, 1992). In contrast, a randomized crossover study of 19 patients comparing ECP with no treatment revealed no statistical difference in skin scores after 1 year of treatment (Enomoto, 1999). A CS of 16 patients treated with 12 ECP procedures (two consecutive days every 6 weeks) reported decreased dermal thickness and increased joint mobility (Papp, 2012). In a long-term follow-up study from the same group, those immunomodulatory effects of the ECP treatment last for 1 year only (Papp, 2016). The timing and indication for TPE and ECP in treating systemic sclerosis have not been well established.

Technical notes

Volume treated: TPE: 1-1.5 TPV; ECP: Typically, MNCs are obtained from processing 1.5L of whole blood, but the volume processed may vary based on patient weight and HCT. The 2-process method collects and treats MNCs obtained from processing 2 TBV.

Frequency: TPE: 1- 3/wk; ECP: Two procedures on consecutive days (one series) every 4-6 wk for 6-12 months

Replacement fluid: ECP: NA; TPE: Albumin

Duration and discontinuation/number of procedures

TPE courses vary widely. A course of six procedures over the 2-3 weeks should constitute a sufficient therapeutic trial. Four weekly TPE treatments had been reported to result in long-lasting improvements in symptoms. Long-term TPE (2-3 weekly for 2 weeks, 1 TPE weekly for 3 months, and

1 TPE every other week as a maintenance therapy) was also used. In the scleroderma renal crisis study, TPE was discontinued when renal function (Cr < 300 mmol/L and serum urea <15 mmol/L) remained stable for at least one month or when the patient required dialysis (Cozzi, 2012). ECP course is longer; a 6-month trial may be considered. If no response is noted, ECP treatment intervals should be increased or stopped completely.

Keywords: systemic sclerosis, scleroderma, CREST, plasma exchange, extracorporeal photopheresis

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SEPSIS WITH MULTIORGAN FAILURE

Incidence: Severe sepsis in adults 300/100,000/yr (US); 8% prevalence in pediatric intensive care		**Procedure**	**Recommendation**	**Category**
		TPE	Grade 2B	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	4(194)	6(215)	16(1,216)	NA

Description of the disease

Sepsis is a systemic inflammatory response to infection in which multiple toxic mediators cause tissue injury, multiple organ dysfunction (MODS), disseminated intravascular coagulopathy (DIC), and relative immune dysregulation. Based on US hospital data from 2004-2009 the incidence of sepsis was 300-1,031/100,000/year with 15-30% mortality. In studies from seven high income countries from 1979-2015, the incidence of severe sepsis was 270/100,000/year with 26% mortality. Risk factors for sepsis include age extremes, chronic medical conditions, immune compromise, indwelling catheters and devices, and disruption of natural defense barriers. Sepsis is a complex process consisting of activation of a variety of host defense systems. Cytokines and other mediators including tumor necrosis factor (TNF), interleukins, leukotrienes, prostaglandins, endotoxin, and transforming growth factor-β (TGF-β) are part of the inflammatory state in sepsis. Coagulopathy, microvascular occlusion, and tissue ischemia appear to be connected to derangements in the balance of a disintegrin and metalloprotease with thrombospondin motifs-13 (ADAMTS13) and von Willebrand factor multimers.

Current management/treatment

Management includes antimicrobial agents, control of the source of the infection, and hemodynamic support including volume, vasopressors, and ventilator support. Additional treatments including corticosteroids, IVIG, anticoagulation, and immunomodulatory agents have been utilized; however, there is not broad acceptance of any one of these therapies.

Rationale for therapeutic apheresis

TPE is postulated to improve organ function by removing inflammatory and antifibrinolytic mediators and replenishing anticoagulant proteins and ADAMTS13, to reverse the pathobiological derangement and restore hemostasis. Observational studies of TPE observed survival rates of 60-87% compared to predicted or historical controls with survival rates of 20-40%. Several CS suggest early treatment is beneficial compared to delayed initiation of therapy, and that TPE may lead to hemodynamic stabilization. A retrospective cohort in 42 pediatric patients found improvement in 28-day mortality, after controlling for illness severity (Sevketoglu, 2014). The Pediatric Health Information System prospective registry of more than 49,000 pediatric patients with sepsis observed 2% were treated with TPE. Mortality was higher in the TPE treated group (32%) versus the untreated group (14%), which was still significant after controlling for patient characteristics, comorbidities, and organ dysfunction [OR = 1.87, 95% CI (1.59-2.20), $p < 0.001$] (Lima, 2018). A multicenter observational longitudinal cohort study in children found TPE was associated with reduced 28-day mortality by multivariate analysis [adjusted relative risk = 0.45, 95% CI (0.23-0.90), $p = 0.02$] and by propensity score weighting [adjusted relative risk = 0.46, 95% CI (0.22-0.97), $p = 0.04$] and improved PELOD scores from baseline (Fortenberry, 2018).

Unlike the observational studies suggestion of efficacy, RCTs have been conflicting. Four RCTs of 10-106 patients using TPE have been published. The largest RCT conducted in patients 17-70 years employed a single TPE with 1 additional TPE the next day if there was no improvement (Busund, 2002). The authors found a 28-day mortality rate of 33% in the treatment and 54% in control ($p < 0.05$). When controlled for other contributing factors, the significance of the effect of TPE on mortality became a non-significant trend ($p = 0.07$). One RCT used continuous plasma filtration in 22 adults and 8 children (Reeves, 1999). Although there was no difference in mortality, reduction of some acute phase reactants such as C3, C-reactive protein, haptoglobin, and α1-antitrypsin was achieved. In a 48 patient RCT of adults and children which compared plasma filtration to standard therapy, there was no significant difference in 28-day mortality; the study closed early due to poor enrollment (Long, 2013). One RCT enrolled 10 children with thrombocytopenia associated multi-organ failure (TAMOF) and culture positive sepsis and randomized them to TPE or standard treatment (Nguyen, 2008). A significant decrease in organ severity scores (PELOD, PEMOD, OFI, $p < 0.001$) and improved 28-day survival (control group 1/5 survived versus TPE group 5/5 survived, $p < 0.05$) was seen in the TPE treated group, who received median of 12 days of TPEs, leading to the trial being stopped early due to improvement in treatment group. Although 2 of 4 studies did not meet enrollment, making interpretation difficult, they were collectively analyzed in a meta-analysis; no association with overall mortality was found with TPE. There was an association for decreased mortality in the adult subgroup (not pediatric), suggesting a relatively high likelihood of bias (Rimmer, 2014).

Technical notes

Centrifugal based and filtration-based instruments have been used. TPE has been used for menigococcal septicemia in several CS and CRs. Patients presenting with meningococcal septicemia, in particular with DIC, could be evaluated for early TPE. In addition to TPE, other blood purification techniques have been used in sepsis, including hemoperfusion with selective removal columns for endotoxin (e.g., polymyxin B and immobilized human serum albumin) and cytokines (e.g., biocompatible porous polymer beads), hemofiltration, and hemodiafiltration. In RCTs, hemoperfusion with polymyxin B was typically performed 1-2 times per patient (Kuriyama, 2018). Meta-analysis of non-RCTs and RCTs with polymyxin B hemoperfusion found an overall reduction in mortality (Chang, 2017), but when only RCTs were analyzed, no impact on 28-day mortality was observed (Kuriyama, 2018). Use of tandem procedures in line with extracorporeal membrane oxygenation (ECMO), especially in pediatrics, has been reported.

Volume treated: 1-1.5 TPV **Frequency:** Daily

Replacement fluid: Plasma

Duration and discontinuation/number of procedures

TPE treatments ranged from 1-2 up to 14 days or resolution of symptoms.

Keywords: plasma exchange, sepsis

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SICKLE CELL DISEASE, ACUTE

Incidence: 273/100,000 (1/375 for Hb SS, 1/835 for Hb SC, 1/1667 for Hb S/ß-thalassemia)	Indication	Procedure	Recommendation	Category
	Acute stroke	RBC exchange	Grade 1C	I
	Acute chest syndrome, severe	RBC exchange	Grade 1C	II
	Other complications*	RBC exchange	Grade 2C	III
# reported patients: >300**	**RCT**	**CT**	**CS**	**CR**
Acute stroke	0	1(52)	8(170)	NA
Acute chest syndrome	0	2(121)	15(160)	NA
Priapism	0	0	2(23)	1(1)
Multisystem organ failure	0	0	3(10)	3(1)
Hepatic sequestration/intrahepatic cholestasis	0	0	1(52)	3(4)
Splenic sequestration	0	0	3(204)	NA

*Includes priapism, multiorgan failure, splenic/hepatic sequestration and intrahepatic cholestasis.
**Includes patients who received RBC transfusion, manual RBC exchange or automated RBC exchange.

Description of the disease

Sickle cell disease (SCD) affects approximately ~100,000 people in the US. It is caused by abnormal sickle hemoglobin, (HbS) that is formed by the substitution of valine for glutamic acid at β6. HbS polymerizes upon deoxygenation, causing RBCs to become rigid and deformed; sickled RBCs occlude the microvasculature leading to tissue hypoxia and infarction. HbS RBCs have a shortened lifespan (~10-20 days), resulting in chronic hemolytic anemia. The overall mortality rate from SCD is ~3% (0.5 deaths/100-person years) with the peak at 1-3 years. The average life expectancy is ≥50 years. The leading causes of death are sepsis, acute chest syndrome (ACS), stroke, acute multiorgan failure (MOF), and pulmonary hypertension. The use of penicillin has increased life expectancy.

Acute manifestations of SCD are vaso-occlusive crisis (VOCs), including stroke, ACS, priapism, splenic sequestration, hepatic/cholestatic, and renal dysfunction. In the absence of preventative therapies, ischemic stroke can occur in up to 10% (overt stroke) or 20-35% (silent stroke) of patients, with a recurrence rate of 46-90%. Patients of HbSS and HbSß0 are at the highest risk. ACS is defined by sudden decreased oxygen saturation despite oxygen therapy in the setting of new infiltrate on chest x-ray, often accompanying fever, tachypnea, coughing, and chest pain. The incidence is highest in young children (2-5 years). ACS is likely due to RBC sickling in the pulmonary vascular space; it can be idiopathic or associated with infection, pulmonary infarction, or fat embolism. Priapism (painful sustained erection >4 hours) can affect up to 35% of male SCD patients. Other acute manifestations of SCD that occur rarely are multiorgan failure (MOF), splenic/hepatic sequestration, and intrahepatic cholestasis.

Current management/treatment

Primary and secondary stroke prevention has resulted in marked stroke rate reduction (see Sickle cell disease non-acute fact sheet), but residual risk exists. When patients present with signs of neurologic or mental status changes, imaging studies should be urgently performed. If stroke is confirmed, emergent RBC exchange should be performed. The treatment for ACS includes supportive care including antibiotics (cephalosporin, macrolide), oxygen (target ≥95% SaO_2), and close monitoring. If Hb level is ≥1 g/dL below baseline and <9 g/dL, transfuse RBCs. For rapid symptom or clinical progression (SaO_2 ≤90%), perform an emergent RBC exchange. Priapism should be treated with vigorous hydration and analgesia and consultation with urologist if symptoms do not improve. RBC transfusion may be used pre-operatively if surgical intervention is needed. Small studies have reported that RBC exchange resolved priapism within 24-48 hours. MOF presents as unexpected life-threatening VOC involving the lung, liver, and kidney. Management includes expedient evaluation and support of vital functions (ventilation, hemodialysis), and RBC transfusion or RBC exchange.

A small CS reviewed 4 patients with SCD and MOF initially treated with RBC exchange (Louie, 2018). After no improvement, TPE was performed. Clinical improvement was observed in 3 of 4 patients. Splenic/hepatic sequestration and intrahepatic cholestasis management includes hydration and surgical consult, and simple transfusion or RBC exchange. In these cases, RBC transfusion or RBC exchange resulted in a better outcome in 11 patients (0% compared to 20% mortality with historical controls).

Rationale for therapeutic apheresis

In acute manifestations of SCD, the decision to use RBC transfusion, manual or automated RBC exchange is guided by the balance of patient's condition, and ability to obtain apheresis services, adequate intravenous access, and blood products quickly, versus the risk of apheresis itself. RBC exchange offers more efficient and rapid removal of HbS RBCs and keeps the patient isovolemic. For patients with their first stroke, exchange (manual or RBC exchange) appears to result in a lower rate of stroke recurrence compared to those treated with RBC transfusion [21% (8/38) versus 57% (8/14), respectively]. A retrospective review of 81 pediatric patients with ACS found that therapy with RBC exchange in the children with worse pulmonary function equalized them to achieve a similar trajectory of care (hospital course) to those children with less severe pulmonary function at the start of the admission. A small study of 5 sickle cell patients showed that the median time to oxygen saturation recovery on room air was 24 hours after RBC exchange (Aneke, 2016). The side effects of RBC exchange in acute SCD manifestations include central venous catheter thrombosis and hemorrhage, which can be mitigated with placement in internal jugular site compared to the femoral vein location, and hyperhemolysis, which is a rare hemolytic reaction. Two studies have also described acute differences in natural anticoagulants, plasma markers of systemic hypoxemia, and red blood cell metabolism after red cell exchange in patients with sickle cell disease (Culp-Hill 2018; Sharma 2018).

Technical notes

Apheresis practitioners should decide the target HCT and either the desired FCR (fraction of patient's RBCs remaining at end of procedure) OR the target volume to be exchanged. In general, it is best to determine the FCR required to achieve target HbS of <30% (or HbS + HbC of 30%, etc.) at the end of the procedure. The end HCT should be 30 ± 3% (≤33% to avoid hyperviscosity), as clinically indicated (Biller 2018). Once these parameters are decided, the apheresis machine will determine the volume necessary to exchange. Patients with unstable blood pressure may not tolerate RBC exchange.

Volume treated: Volume necessary to achieve target HbS level	**Frequency:** One procedure
Replacement fluid: RBC units, HbS negative, leukocyte reduced, antigen-matched (e.g., C/c, E/e, K)	

Duration and discontinuation/number of procedures

For an acute situation, typically one procedure is necessary to achieve desired HbS level.

Keywords sickle cell disease, red blood cell exchange, transfusion, stroke, acute chest syndrome, priapism, multiorgan failure

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SICKLE CELL DISEASE, NON-ACUTE

Incidence: 273/100,000 (1/375 for Hb SS, 1/835 for Hb SC, 1/1667 for Hb S/ß-thalassemia)	Indication	Procedure	Recommendation	Category
	Stroke prophylaxis	RBC exchange	Grade 1A	I
	Pregnancy	RBC exchange	Grade 2B	II
	Recurrent vaso-occlusive pain crisis	RBC exchange	Grade 2B	II
	Pre-operative management	RBC exchange	Grade 2A	III
# reported patients: >300*	**RCT**	**CT**	**CS**	**CR**
Stroke prophylaxis	2(326)	1(36)	NA	NA
Pregnancy	0	5(170)	1(5)	NA
Recurrent vaso-occlusive pain crisis	1(130)	1(21)	5(45)	NA
Pre-operative management	3(1035)	4(184)	NA	NA

*Includes patients who received RBC transfusion, manual RBC exchange or automated RBC exchange.

Description of the disease

Sickle cell disease (SCD) affects approximately ~100,000 people in the US. It is caused by abnormal sickle hemoglobin, (HbS) that is formed by the substitution of valine for glutamic acid at β6. HbS polymerizes upon deoxygenation, causing RBC to become rigid and deformed; sickled RBCs occlude the microvasculature leading to tissue hypoxia and infarction. HbS RBCs have a shortened lifespan (~10-20 days), resulting in chronic hemolytic anemia. The overall SCD mortality rate is ~3% (0.5 deaths/100-person years) with peak at 1-3 years. The average life expectancy is ≥50 years. Leading causes of death include sepsis, acute chest syndrome (ACS), stroke, acute multiorgan failure (MOF), and pulmonary hypertension (PH).

Chronic complications of SCD can begin in early age. These include recurrent vaso-oclusive crisis (VOC), end organ damage, avascular necrosis of bones, cholelithiasis, and pulmonary hypertension. Complications from chronic therapy, such as iron overload and alloimmunization, are also common, particularly from simple blood transfusions. Chronic VOC (>3 months) occurs in up to 55% of SCD patients with PH occurring in 6-10%. If chelation therapy is not used, many chronically transfused patients with SCD may become iron overloaded.

Current management/treatment

RBC transfusion is one of the mainstays of long-term SCD therapy and supported by multiple RCTs. For stroke prevention there are several important studies. The STOP trial randomized children with elevated blood flow velocity, which predicts stroke risk, to standard supportive care without transfusion (control) versus chronic monthly transfusion for primary stroke prevention (Adams, 1998). The trial was terminated prematurely due to the marked (90%) stroke risk reduction by chronic transfusion. Another trial found that chronic RBC transfusion also was efficacious in secondary stroke prevention/progression in children with evidence of silent cerebral infarct on imaging (DeBaun, 2014). Transfusion withdrawal is associated with an increased risk of recurrent stroke.

In the setting of chronic transfusion therapy during which time the patient is clinically stable, targeting a pre-transfusion threshold of 50% HbS may be as effective as 30%. Several studies have shown decreased frequency of recurrent VOC with monthly manual RBC exchange. Surgery is associated with high rates of SCD related complications. The TAPS RCT demonstrated that pre-op transfusion was associated with decreased perioperative complications (39% non-transfused vs 15% transfused; Howard, 2013). Pre-op transfusion should target a Hgb of 10 g/dL. For patients with high baseline Hgb such as in HbSC or HbSb1, RBC exchange may be used to avoid elevated blood viscosity, especially for high risk procedures (neurosurgery, prolonged anesthesia, cardiac bypass procedures). Hydroxyurea (HU), which increases HbF%, is another SCD therapy. HU reduces frequency of VOC episodes, ACS, and other complications, and is associated with less transfusion and hospital admissions. In pediatric patients with previous stroke, the SWiTCH RCT showed that HU therapy plus phlebotomy is not able to replace chronic RBC therapy for secondary stroke prevention (Ware, 2011). However, the TWiTCH trial demonstrated that HU can substitute for chronic transfusions to maintain TCD velocities in patients with abnormal TCD velocities and prevent primary stroke (Ware, 2016). Hematopoietic stem cell transplantation is a potentially curative therapy, however, indications, appropriate donor sources and preparative regimens are being defined to optimize outcomes.

Rationale for therapeutic apheresis

Studies have shown automated RBC exchange results in a more efficient removal/replacement of HbS RBCs than manual exchange or simple transfusions. RBC exchange may also have beneficial effects on blood viscosity, vessel relaxation time, and reduction of adhesion molecule level like sVCAM-1. One report suggests that RBC exchange reduces cerebral blood flow and oxygen extraction fraction relieving cerebral metabolic stress mitigating infract risk (Guilliams, 2018). Although iron overload can be treated with chelation or phlebotomy, its effectiveness has been limited by poor compliance. RBC exchange, particularly in conjunction with isovolumic hemodilution, can remove or keep iron stores steady. The 2015 ASFA Red Blood Cell Exchange consensus conference supports RBC exchange with and without isovolemic hemodilution to reduce or prevent iron overload. In 36 pediatric patients, long-term RBC exchange for a mean of 5 years was associated with improved growth velocity without increased risk of iron overload compared to matched controls (Bavle, 2014).

Chronic RBC exchange has also been described in several clinical settings. In pregnancy, RBC transfusion, and RBC exchange have been reported to be associated with lower risk of maternal and neonatal mortality, intrauterine growth restriction and other fetal complications, and decreased rate of maternal complications, although larger comparative studies are needed. RBC exchange has also been used to manage PH improving SaO2 and ability to execute activities of daily life.

Technical notes

Chronic vascular access remains a concern in RBC exchange (Otrock, 2018). Vortex ports have been used successfully in adults though with longer procedures and more complications. A CS demonstrated feasibility with arterior-venous fistulas for long term access, but the risk/benefits need to be discussed (Delville, 2016). Apheresis equipment calculates the replacement RBC volume to achieve target HbS (fraction of RBCs remaining at procedure end) and HCT. General guidelines are: (1) end HCT at 30+/-3% (<33-36% to avoid hyperviscosity) and (2) HbS of 30% (or HbS+HbC of 30%, etc.). Modification of RBC exchange utilizing isovolemic hemodilution, which consists of RBC depletion with 0.9% NaCl replacement followed by standard RBC exchange, reduces replacement RBC volume and donor exposure, helping decrease transfusion related iron overload.

Volume treated: Volume necessary to achieve target HbS level	**Frequency:** As needed to maintain target HbS level
Replacement fluid: RBC units, HbS negative, leukocyte reduced, antigen-matched (e.g., C/c, E/e, K)	

Duration and discontinuation/number of procedures

Duration and number of RBC exchanges depend upon clinical indications; one time for pre-op, variable times for chronic pain, and life-long for stroke prevention.

Keywords: sickle cell disease, red blood cell exchange, transfusion, stroke, iron overload, pregnancy

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STEROID-RESPONSIVE ENCEPHALOPATHY ASSOCIATED WITH AUTOIMMUNE THYROIDITIS (HASHIMOTO'S ENCEPHALOPATHY)

Incidence: Rare		**Procedure**	**Recommendation**	**Category**
		TPE	Grade 2C	II
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	0	22(24)

Description of the disease

Hashimoto's encephalopathy (HE), also known as steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), is a rare neuropsychiatric syndrome best defined by encephalopathy of unknown etiology associated with the high titers of antithyroid antibodies in the absence of alternative diagnoses such as nervous system infection, tumor or stroke. The clinical presentation is highly variable, usually acute or subacute. There are typically two distinct presentations. For most patients (~75%), it may present as an indolent form associated with depression, confusion, cognitive decline, myoclonus, tremors, and fluctuations in level of consciousness. This form is commonly associated with a more progressive disease. The less common type is an acute onset of episodes of stroke-like symptoms, seizure, and psychosis, and this presentation is usually associated with a relapsing-remitting course. The mean age of onset is about 40-50 years and like most autoimmune disorders, females are affected more than men (4:1). Imaging, EEG, and cerebrospinal fluid studies are usually non-specific but can help to rule out other causes of encephalopathy. Despite the elevated levels of antithyroid antibodies, most patients are euthyroid at the time of diagnosis. The most common antithyroid antibody detected is antithyroid peroxidase (anti-TPO), followed by antithyroglobulin antibodies; however, these are not specific for this diagnosis. As such, the role of the antithyroid antibodies as the primary cause of Hashimoto's encephalopathy is controversial. Furthermore, the titer of antithyroid antibodies does not correlate well with clinical symptoms of the disease or with its severity. However, persistent elevated titers of the antithyroid antibodies appear to be predictive of relapse, a prolonged disease course, less response to steroids, and a worse prognosis. Other biomarkers include anti-alpha-enolase antibody, which has been shown to increase in 68-83% of diagnosed HE patients.

Current management/treatment

High dose corticosteroids are the first line therapy, with 88% of cases achieving response. Common steroid regimens include IV methylprednisolone (500-1000 mg/day) and oral prednisone (1-2 mg/kg/day), each either alone or combined (IV followed by oral therapy), which is tapered within weeks or months, according to clinical response. For patients who fail initial therapy with steroids or relapse, secondary therapies, such as immunosuppressive agents, have been used with variable efficacy. IVIG for steroid unresponsive patients has shown successful clinical response in some CRs. Azathioprine or cyclophospamide after steroid pulse therapy has also been successful. Rituximab has been utilized to reduce the breakthrough events in patients with HE. Recently, levetiracetam, a new anti-epileptic medication that has anti-inflammatory effect, has been reported to be effective in 2 cases.

Rationale for therapeutic apheresis

Although the pathogenesis is unknown, an autoimmune process is believed to play a role. In the published cases to date, TPE had been performed, in both adult and pediatric cases, in patients who have failed to respond to steroids with most patients demonstrating symptomatic improvements.

Technical notes

Volume treated: 1-1.5 TPV	**Frequency:** Daily to every other day
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

The published CRs used 3-9 procedures, mostly commonly 5.

Keywords: Hashimoto encephalopathy, antithyroid antibodies, Steroid-responsive encephalopathy associated with autoimmune thyroiditis, plasma exchange

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STIFF-PERSON SYNDROME

Incidence: 1/1,000,000		**Procedure**	**Recommendation**	**Category**
		TPE	Grade 2C	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	0	0	6(344)	21(23)

Description of the disease

Stiff-person syndrome (SPS) is a rare acquired, autoimmune neurological disorder characterized by fluctuating muscle rigidity in the trunk and limbs as well as increased sensitivity to noise, touch and emotional distress which can result in muscle spasms. Co-contractions of agonist and antagonist muscles occur with continuous involuntary firing of motor units at rest. Hyperlordosis due to the episodic arching and stiffness of the lumbar spine is a diagnostic hallmark of SPS. SPS is more common in women than men and is often associated with autoimmune diseases including Graves' disease, Hashimoto's thyroiditis, pernicious anemia, and type I diabetes mellitus. Childhood onset as early as one year of age has been reported. Autoantibodies reactive to 65 kDa glutamic acid decarboxylase (GAD65), the enzyme responsible for the synthesis of GABA in the brain and pancreatic islet cells, are present in the serum in up to 90% of patients with SPS. These antibodies block GABA synthesis. Presentations may vary from a partial form to a rapidly progressive form known as progressive encephalomyelitis with rigidity and myoclonus (PERM). Seronegative individuals for GAD65 are more likely to have a coexisting cancer (25% versus 4%), including breast, colon, small cell lung cancer, Hodgkin's lymphoma and malignant thymoma. The paraneoplastic form of the syndrome is associated with autoantibodies to the 128 kDa synaptic protein amphiphysin.

Current management/treatment

Treatment is with a variety of medications including immune therapies, anti-anxiety medications, muscle relaxants, anticonvulsants and pain relievers. Diazepam, a benzodiazepine that diminishes continuous motor unit activity through inhibition of central catecholamine neurons and activation of GABAnergic neurons, is given to decrease rigidity and spasms. Baclofen, a GABA-B agonist, valproate, and clonazepam are also used. Intrathecal baclofen administered via constant-infusion pump has shown efficacy. High-dose IVIG (2 gm/kg per month in two consecutive daily doses of 1 gm/kg) is effective in relieving symptoms of stiffness and spasticity, and in reducing the titer of anti-GAD65 antibodies. Other immunosuppressive treatment, such as rituximab, has been tried with variable effect and is often considered when traditional immune therapy and antispasmodics have been ineffective.

Rationale for therapeutic apheresis

The association of specific autoantibodies with SPS has led to scattered CRs, both with positive and negative results, and a few small CS describing responses to TPE in conjunction with other immunosuppressive therapies. There are no RCT data. One CR demonstrated the association between the decline of Ab level and the timing of TPE and its treatment response (Farooqi, 2015). In all reported patients who received TPE, 50-60% has had some degree of response.

Technical notes

TPE can effectively deplete normal immunoglobulins when enough plasma volumes are exchanged in a brief period. If TPE is to be offered to a patient with SPS the patient should be made aware of the paucity of clinical data to support its use and of the availability of IVIG as an alternative. If IVIG is not available, then it may be reasonable to proceed with TPE. TPE may also be considered if the patient does not respond to conventional therapy. TPE should be used as an adjunct with standard pharmacological therapy.

Volume treated: 1-1.5 TPV	**Frequency:** Every 1-3 days
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

A series of 4-5 TPEs of 1-1.5 TPV that is typically performed over 8-14 days. Repeat series of TPE can be employed empirically if there is an objective clinical improvement that is followed by a relapse of symptoms. Successful use of TPE for chronic treatment has also been reported.

Keywords: Stiff-person syndrome, Stiff-man syndrome, progressive encephalomyelitis with rigidity and myoclonus, plasma exchange, apheresis

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SUDDEN SENSORINEURAL HEARING LOSS

Incidence: 15-30/100,000		**Procedure**	**Recommendation**	**Category**
		LA/RheopheresisTPE	Grade 2A	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
LA*	4(390)	0	NA	NA
Rheopheresis	1(240)	1(52)	3(43)	NA
TPE	0	0	1(16)	1(1)

*HELP-apheresis

Description of the disease

Sudden hearing loss is defined as subjective hearing impairment in one or both ears that occurs over a 72- hour period. Idiopathic sudden sensorineural hearing loss (SSHL) is usually unilateral (>90%) and can range from mild to total. SSHL typically exhibits hearing loss of at least 30 decibels affecting at least 3 consecutive frequencies in the standard pure tone audiogram, usually defined in relation to the opposite ear's thresholds. It has equal gender distribution and wide age distribution (average 50- 60 years). Hearing loss may be accompanied by tinnitus (80%), aural fullness (80%) and vertigo (30%). Clinical presentation has some overlap with the diagnosis of autoimmune ear disease (AIED), for which subacute presentation is more common. SSHL is a complex disease influenced by interactions between multiple internal and external pathogenic factors, e.g., noise, heredity and environment, infection, vascular impairment of inner ear blood flow in the terminal labyrinthine artery, ototoxicity, trauma, autoimmunity, neoplastic disease, endolymphatic hydrops and central nervous system disease. Hypercholesterolemia and hyperfibrinogenemia are associated with increased risk to develop SSHL, however, no thresholds were confirmed for individual risk assessment.

Current management/treatment

A major issue for any therapeutic intervention for SSHL is the spontaneous early recovery rate in the range of 40-65%. There is no longer a consensus that SSHL must be considered an otological emergency. The current UK guideline recommends steroids to treat adults with SSHL (NICE, 2018). Decreasing inflammation and improving blood flow have been major considerations for existing therapeutic approaches. Pentoxifylline, or intravenous dextran, hydroxyethyl starch, or glycerol were administered to improve RBC flexibility and whole blood viscosity. However, efficacy was never proven convincingly. Current first-line treatment options for SSHL are oral steroids, or intra-tympanic steroid injections or a combination of both. Oral corticosteroids are suggested as an option and not as an explicit recommendation given the variability of evidence and the presence of side effects in systemic corticosteroid treatment. In AIED, corticosteroid therapy is the therapy of choice.

Hyperbaric oxygen therapy is also discussed as an option for the management of SSHL, based on the hypothesis to improve microcirculation by increasing tissue oxygen levels. However, there is no strong evidence base, it is not widely available, expensive and has potential adverse effects.

Rationale for therapeutic apheresis

Improvement of inner ear microcirculation and hair cell function by acute reduction of fibrinogen and cholesterol levels were the pathogenic mechanisms guiding the approach to use apheresis, in particular HELP-apheresis or rheopheresis as treatment for SSHL. Elevated fibrinogen and LDL cholesterol were identified as pathogenic factors at molecular levels, however, further analysis failed to confirm that thresholds might be helpful for the indication of apheresis.

Two adequately powered multicenter RCTs, each enrolling more than 200 patients <7 days since onset of SSHL, evaluated HELP-apheresis (1 treatment) and rheopheresis (2 treatments) for SSHL (Mösges, 2009; Suckfüll, 2002). In the HELP-apheresis trial the control group received 250 mg prednisolone, tapered in 25 mg steps, 500 ml hydroxiethyl starch and 400 mg pentoxifylline for 10 days. In the rheopheresis trial the control group received either 250mg methyl-prednisolone for 3 days with following stepwise reduction, or 500 ml hydroxyethyl starch plus 600 mg pentoxifylline for 10 days. Both trials could not demonstrate superiority in their apheresis arms after 48 hours or at 10 days. Another RCT (n=132) investigated a single HELP-apheresis additional to 500 mL glycerol and 8 mg dexamethasone for 10 days (Bianchin, 2010). Statistically significant and clinically relevant hearing recovery was seen in standard treatment plus HELP group at 24 hours (75% vs. 41%) and 10 days (76% vs. 45%). An important factor for this positive result might be, that patients' onset of SSHL was 12-13 days before treatment, thus reducing the amount or spontaneous recovery in enrolled patients. In patients who failed to respond to standard therapy, HELP-apheresis or rheopheresis demonstrated clinically significant improvement of hearing in more than half of the patients. The time window to expect clinically relevant benefit seemed to span 6 weeks since onset of SSHL (Heigl, 2009). Experience with TPE, or fibrinogen plasma adsorption is limited to very few patients.

Technical notes

Patients with LDL cholesterol or fibrinogen elevations respond to apheresis treatment more rapidly and with greater improvement. Specific trigger levels have not, however, been suggested. Longer time between symptom onset and treatment is associated with poorer hearing recovery.

Volume treated: TPE, HELP-apheresis, Rheopheresis: 1 TPV	**Frequency:** HELP-apheresis, Rheopheresis: 1-2 treatments; TPE, fibrinogen adsorption; 1-3; treatments performed on consecutive days or with 1 day intervals.
Replacement fluid: TPE: Albumin; None for selective methods.	

Duration and discontinuation/number of procedures

Procedures with all methods were mostly performed on consecutive days, depending upon response as determined by standard audiometry. There is no experience with increasing numbers of treatments over a longer period of time.

Keywords: plasma exchange, lipid apheresis, sudden sensorineural hearing loss, sudden deafness, rheopheresis, fibrinogen, tinnitus

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SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Prevalence: 1-2/1000	**Indication**	**Procedure**	**Recommendation**	**Category**
	Severe complications	TPE	Grade 2C	II
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Severe complications	1(20)	2(108)	15(148)	NA

Description of the disease

Systemic lupus erythematosus (SLE) is an incurable chronic, remitting, and relapsing illness, which typically affects multiple tissues and organs. SLE is more prevalent in women than men across all age groups and populations; the female-to-male ratio is highest at reproductive age, ranging between 8:1 and 15:1, and is lowest in pre-pubertal children at about 4:3. The prevalence of SLE and the chances of developing lupus nephritis (LN) vary considerably between different regions of the world and different races and ethnicities. Clinical symptoms are non-specific (fatigue, malaise, fever, anorexia, nausea, weight loss) and/or attributable to the involvement of one or more organ systems. LN is a major risk factor for morbidity and mortality in SLE and 10% of patients with LN will develop end stage renal disease (ESRD). Many patients present with LN as initial manifestation. It is currently not possible to determine a priori who with SLE will develop LN. Immunologic abnormalities are a prominent feature of the disease, including the production of antinuclear antibodies (ANA) and anti-dsDNA. Pathogenesis involves circulating autoantibodies, immune complexes, and complement deposition leading to cell and tissue injury. Nucleosomes are presented as autoantigens to pathogenic T helper and B cells and T regulatory cells are significantly decreased. Defects in apoptosis are also postulated to occur. Low complement levels and high titers of autoantibodies suggests active disease. Screening tests include anti-dsDNA antibodies and ANA, antiphospholipid antibodies and complement levels. When the ANA is positive, or there is strong clinical suspicion for SLE, additional testing for anti-Sm, Ro/SSA, La/SSB, and U1 ribonucleoprotein (RNP) is recommended. Persistent antiphospholipid antibodies and thrombotic or obstetrical events, such as recurrent pregnancy loss, may indicate a secondary antiphospholipid syndrome (APS).

Current management/treatment

Therapy entails conventional immunosuppressive agents (cyclophosphamide, azathioprine, prednisone, methotrexate, cyclosporine and mycophenolate mofetil) and newer biologic therapies (rituximab, belimumab). Autologous hematopoietic stem cell transplantation has been used as a salvage therapy in select patients. In general, intensity of treatment is guided by the most severe organ involvement. The overarching goal of LN treatment is to prevent CKD and ESRD. Several scoring systems are available to determine disease activity and therapy efficacy in SLE, but the SLE Disease Activity Index (SLEDAI) and the British Isles Lupus Assessment Group (BILAG) are the most frequently used in RCTs and observational studies. The SLEDAI consists of 24 items (present or absent) representing nine organ systems. SLEDAI score ≥6 defines active disease (Bombardier, 1992). The BILAG contains 86-questions covering 8 organ systems which requires an assessment of improved (1), the same (2), worse (3), or new (4) over the last month. Scores are converted to an A-E alphabetical assessment that provides treatment recommendations (Symmons, 1988).

Rationale for therapeutic apheresis

TPE was initially used to treat SLE under the assumption that removing pathogenic autoantibodies and immune complexes would control disease activity. However, the first RCT in mild SLE, where the patients underwent six 4L exchanges within 2 weeks with expected autoantibody and immune complex reductions, showed no clinical improvement (Wei, 1983). TPE in LN has previously been classified as category IV (see previous edition) based on a RCT of TPE plus prednisone and cyclophosphamide versus prednisone and cyclophosphamide that showed no benefit in the TPE arm (Lewis, 1992). Further smaller trials since then supported these findings. Plasma exchange is not currently among induction or maintenance therapy guidelines for treatment of LN but is mentioned in current European guidelines as a treatment option in the setting of pregnancy or rapidly progressive glomerulonephritis (Bertsias, 2012).

TPE may also be a treatment option for patients with severe, refractory disease manifestations (diffuse alveolar hemorrhage, thrombotic microangiopathy, hyperviscosity, cryoglobulinemia, and CNS involvement). Current British Society for Rheumatology guideline recommendations support the use of TPE in patients with refractory cytopenias, thrombotic thrombocytopenic purpura (TTP), severe neurologic involvement and catastrophic APS (Gordon 2018). A review of 26 patients with SLE and CNS involvement who were treated with TPE or TPE/cyclophosphamide revealed that 74% of patients improved, 13% stabilized, and 13% progressed (Neuwelt, 2003). Another retrospective review of 20 patients with severe complications of SLE (including LN (8), bleeding related to thrombocytopenia (4), renal failure (2), alveolar hemorrhage (2), TTP (1), pulmonary fibrosis (1), psychosis (1) and neuromyelitis optica (1)) concluded that TPE might be useful as a concurrent therapy in severe cases while waiting for immunosuppressive therapy to take effect (Soyuöz, 2018). In addition, there are multiple well-documented CRs of beneficial effect of TPE in SLE associated TTP, myasthenia gravis, hyperviscosity, catastrophic APS, and cryoglobulinemia. There are data on use of IA and DFPP for severe refractory cases. A RCT in severe LN suggested that adjunctive IA and TPE were equally effective in reducing SLEDAI scores (Loo, 2010).

Technical notes

Volume treated: 1-1.5 TPV	**Frequency:** LN or DAH: daily or every other day; Other severe complications: 1-3 times per week
Replacement fluid: Albumin, plasma	

Duration and discontinuation/number of procedures

Typically course of 3-6 TPE is enough to see response in the patients with severe complications of SLE. Prolonged treatments have been reported but efficacy and rationale behind this approach is questionable.

Keywords: systemic lupus erythematosus, lupus nephritis, central nervous system lupus, plasma exchange, immunoadsorption

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THROMBOCYTOSIS

Incidence: ET: 0.2-2.5 per 100,000/yr; PV: 0.2-2.3 per 100,000/yr	Indication	Procedure	Recommendation	Category
	Symptomatic	Thrombocytapheresis	Grade 2C	II
	Prophylactic or secondary	Thrombocytapheresis	Grade 2C	III
# reported patients: 100-300	**RCT**	**CT**	**CS**	**CR**
Symptomatic	0	0	9(190)	NA
Prophylactic or secondary	0	0	2(39)	3(4)

ET = essential thrombocythemia; PV = polycythemia vera

Description of the disease

Thrombocytosis, defined as a circulating platelet count ≥450 × 10^9/L, is more commonly reactive (i.e., secondary thrombocytosis) to anemia (acute bleeding, hemolysis, iron deficiency), infection, inflammation, asplenia, and/or malignancy. In these clinical scenarios, the patient is not at increased risk of thrombosis or bleeding because, while elevated, the platelets are functionally normal. In contrast, in primary thrombocytosis, such as in myeloproliferative neoplasms (MPN), including essential thrombocythemia (ET), polycythemia vera (PV), chronic myeloid leukemia (CML), pre-fibrotic primary myelofibrosis (PMF), myelodysplastic syndrome, and rarely, acute myeloid leukemia, the platelets are functionally abnormal and thus, thrombocytosis can be associated with thrombohemorrhagic events.

ET is a clonal MPN characterized by autonomous overproduction of platelets. About 90% of patients have mutations in *JAK2* (~55% of patients), calreticulin (*CALR*), or *MPL.* Arterial or venous thromboembolic events include microvascular thrombosis, stroke and transient ischemic attacks, myocardial infarction, venous thromboembolism, and first-trimester pregnancy loss (either spontaneously or during an otherwise hypercoagulable state). The cumulative rate of thromboembolism is 1-3% per patient-year. Older age, presence of *JAK2* mutation, and history of thrombosis and/or cardiovascular risk factors place the patient at high risk for thrombotic complications. ET can also lead to bleeding, which usually occurs in mucocutaneous sites (rarely GI) and affects 1-30% of patients, which is usually due to an acquired von Willebrand syndrome (AVWS). The risk of bleeding increases significantly when the platelet count is >1,000-1,500 × 10^9/L. Risk of hemorrhage and thrombosis also appears to be increased when the white blood cell count is also elevated. If performed, splenectomy can be associated with extreme “rebound” thrombocytosis (>1,000 × 10^9/L) in 5% of cases with postoperative thrombosis (10%) and bleeding (14%); however, platelet count does not predict thrombohemorrhagic complications.

Current management/treatment

Low-dose aspirin is indicated for thromboprophylaxis in low risk patients and is also useful in reducing vasomotor symptoms, such as headache, tinnitus, ocular disturbances and erythromelalgia. Low dose aspirin should not be used in patients with evidence of AVWS; however, it can be used if the ristocetin level is >30%. In high risk patients, cytoreductive therapy with hydroxyurea is indicated. Alternative therapies include interferon-α (which is the treatment of choice in pregnancy) and anagrelide, which associated with an increased risk of post-ET myelofibrosis. There is no difference in the 1-year complete response rate, or rate of thrombosis/hemorrhage or transformation rate at 2 years between ruxolitinib and standard of care. Platelet count should be normalized before surgery, particularly splenectomy, to minimize complications and avoid rebound thrombocytosis. Venous and arterial thromboembolic events are treated in accordance with national guidelines and institutional policy. Patients with extreme thrombocytosis and hemorrhage should be treated to lower the platelet count with medical therapy and/or thrombocytapheresis.

Rationale for therapeutic apheresis

Thrombocytapheresis has been utilized to prevent recurrent or treat acute thromboembolism or hemorrhage in selected patients with MPN and uncontrolled thrombocytosis. CRs describe rapid improvement of symptoms and thrombotic/hemorrhagic complications of the disease that are unresponsive to cytoreduction and other first-line therapies. It has also been used to treat extreme rebound thrombocytosis after splenectomy and, during pregnancy to prevent recurrent fetal loss in high-risk patients with PV or ET; although it is not indicated or beneficial for standard-risk pregnant women. Although the therapeutic mechanisms are not well defined, rapid cytoreduction is believed to ameliorate prothrombotic factors associated with the dysfunctional platelets. Restoring normal platelet count corrects the short plasma half-life of large VWF multimers with ET; and this may be important for patients with AVWS and >1,000-1,500 × 10^9/L platelets. Thrombocytapheresis is only a bridging therapy and thus, maintaining the patient on cytoreduction therapy is essential to prevent platelet rebound after the procedure.

Elective thrombocytapheresis should also be considered for cytoreduction of patients at increased risk of major hemorrhage when hydroxyurea is contraindicated (such as in pregnancy) or in situations rapid reduction is necessary (such as the requirement for emergent surgery). Platelet-lowering agents must be given to prevent rapid re-accumulation of circulating platelets whenever possible. Although anecdotal CRs have described a potential benefit of thrombocytapheresis with secondary thrombocytosis, rationale is undefined and efficacy unproven.

Technical notes

Each procedure lowers the platelet count by ~30-60%. Anticoagulant ratio of whole blood: anticoagulant should be 1:6-12; heparin should be avoided to prevent ex-vivo platelet clumping.

Volume treated: 1.5-2 TBV

Frequency: Daily or as indicated to reach/maintain goal

Replacement fluid: Saline and/or albumin as necessary to maintain the blood pressure

Duration and discontinuation/number of procedures

With acute thrombohemorrhagic events, goal is normalization of platelet count (<350-450 × 10^9/L) and/or resolution of symptoms. It is important to maintain normal count until cytoreductive therapy takes effect. Goal for prophylaxis of high-risk patients who are pregnant, undergoing surgery or postsplenectomy should be determined on case-by-case basis (considering the patient's history of thrombosis or bleeding at a specific platelet count). Without an informative clinical history, platelet count of ≤450-600 × 10^9/L may be enough.

Keywords: Thrombocytosis, essential thrombocythemia, myeloproliferative neoplasm, polycythemia vera, primary myelofibrosis, chronic myeloid leukemia, thrombocytapheresis

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THROMBOTIC MICROANGIOPATHY, COAGULATION MEDIATED

Incidence: Rare	Indication	Procedure	Recommendation	Category
	THBD, DGKE, and *PLG* mutations	TPE	Grade 2C	III
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
THBD mutations	0	0	1(6)	2(2)
DGKE mutations	0	0	0	1(1)
PLG mutations	0	0	0	1(1)

Description of the disease

Thrombotic microangiopathy (TMA) refers to the histopathologic findings of arteriolar microthrombi with associated intimal swelling and fibrinoid necrosis of the vessel wall. A variety of etiologies for this syndrome are now classified. Atypical hemolytic uremic syndrome (aHUS) is most commonly due to genetic mutations of complement and complement regulatory molecules leading to uncontrolled activation of the alternative complement pathway (see Thrombotic microangiopathy, complement mediated fact sheet). This in turn, leads to TMA due to C3 tissue deposition, C5b-9 injury of endothelial cells, kidney injury, and hypertension. However, mutations in complement genes are not always present in those with disease and some with mutations do not appear to have disease, suggesting incomplete penetrance and/or other genetic modifiers of function. Additionally, genetic mutations in proteins of the coagulation cascade are implicated in the clinical syndrome of aHUS. This may be because underlying HUS pathophysiology is due to small vessel thrombosis; thus, genetic mutations of the coagulation proteins may increase the risk of TMA.

Thrombomodulin, *THBD*, is a thrombin cofactor that acts as an anticoagulant and decreases complement factor I (CFI) induced inactivation of C3b. Six different mutations in the *THBD* gene were found in 7 unrelated patients with clinical aHUS defined as ≥1 episode of TMA associated with renal failure and without Shiga toxin (Delvaeye, 2009). These mutations impair the function of thrombomodulin and thus may account for ~5% of the underlying genetic mechanism in aHUS patients. The age range for affected patients with *THBD* mutations is 4-24 years. Patients with *THBD* associated aHUS may have recurrent HUS episodes and normal C3 and C4 levels. Diacylglycerol kinase epsilon, *DGKE*, is a lipid kinase that catalyzes phosphorylation of arachidonic acid containing phosphatidic acid to inhibit protein kinase C. Mutations may lead to a pro-thrombotic state. A study of 9 unrelated kindreds showed that mutations in *DGKE* were found in up to 50% of children presenting with aHUS before 1 year of life and no patients after age 1 year (Lemaire, 2013). There have been other reports of patients with *DGKE* mutations presenting with aHUS within the first year of life, suggesting this represents a distinct subgroup of aHUS (Almoshary, 2017). Plasminogen, *PLG*, is a zymogen that converts to plasmin, a fibrinolytic serine protease that dissolves fibrin. In 4 patients with clinical aHUS, four different *PLG* mutations have been found that suggest plasminogen deficiency and deleterious protein function. Some patients had more than one deleterious genetic mutation. Other deleterious mutations found in aHUS patients include factor mutations (FXII, c1681-1G>A) and von Willebrand factor (c4165G>C and several others).

Current management/treatment

Initial management of coagulation protein gene mutation induced TMA may differ from other aHUS management protocols. Because these genetic mutations are not all directly impactful on the complement cascade, therapy with eculizumab may not be beneficial. In fact, patients with *DGKE* mutations do not appear to benefit from eculizumab therapy, some having acute relapses while on the therapy (Lemaire, 2013). Renal transplantation may be efficacious in *DGKE* patients, as relapses were not seen after transplant (in contrast to complement mediated aHUS patients).

Rationale for therapeutic apheresis

The benefit for TPE or plasma infusion is not consistent in this patient population. Further experience is needed to determine if plasma can be a source for therapeutic intervention, although intuitively, plasma should contain the deficient coagulation factors absent or decreased in affected patients. The largest CS included 13 patients with *THBD* mutation that were part of a larger aHUS registry review (Noris, 2010). Of these 13 patients, 6 patients were treated with plasma therapy (TPE or plasma infusion) for 8 separate episodes, with remission achieved in 7 episodes (88%; 5 complete and 2 partial remissions). One patient died and one went on to develop end stage renal disease. The authors suggest no difference in plasma infusion compared to TPE, although this includes all aHUS patients, not just *THBD* patients.

Technical notes

The specific TPE replacement fluid strategy and frequency are not described. Recommendations are based on published reports to treat complement-mediated TMA.

Volume treated: 1-1.5 TPV	**Frequency:** Daily or every other day
Replacement fluid: Plasma	

Duration and discontinuation/number of procedures

As there is no standardized approach, the duration and schedule of TPE for treatment of thrombotic thrombocytopenic purpura has been empirically adopted in several patients, sometimes while diagnostic evaluation is ongoing.

Keywords: coagulation, thrombotic microangiopathy, atypical HUS, thrombomodulin, diacylglycerol kinase episolon, plasminogen, *DGKE*, *THBD*, *PLG*

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THROMBOTIC MICROANGIOPATHY, COMPLEMENT MEDIATED

Incidence: <7/1,000,000	**Indication**	**Procedure**	**Recommendation**	**Category**
	Factor H autoantibody	TPE	Grade 2C	I
	Complement factor gene mutations	TPE	Grade 2C	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Factor H autoantibody	0	0	5(126)	NA
Complement factor gene mutations*	0	1(31)	22(361)	NA

*These studies include some patients who were not tested or were tested and found negative for complement factor gene mutations.

Description of the disease

Atypical hemolytic syndrome (aHUS), now called complement-mediated thrombotic microangiopathy (TMA) is caused by uncontrolled activation of the alternative complement system. It can manifest like infection associated HUS, but may have a chronic, progressive course, punctuated by catastrophic events such as acute kidney injury, retinal thrombosis, stroke, hepatitis, pancreatitis, diarrhea, pulmonary hemorrhage, and peripheral thrombosis. The rates of mortality and progression to end stage renal disease (ESRD) are approximately 25% and 50% respectively; however, rates may be improving in the eculizumab era. Incomplete forms with mild or no typical hematologic features, account for ~20% of cases. Disease may present with an insidious onset at any age, but many cases present in the first few months of life and 40% occur in young adults.

A growing list of genetic mutations and polymorphisms, primarily involving complement regulatory proteins, predispose to complement-mediated TMA. The primary pathogenic event appears to be endothelial injury leading to formation of platelet-fibrin hyaline microthrombi, which occlude arterioles and capillaries. Approximately 60% of cases involve genes encoding complement regulators [factor H (*CFH*), membrane cofactor protein (MCP) (*CD46*), and factor I (*CFI*)] or complement activators [factor B (*CFB*) and complement component C3 (*C3*)]. CFH mutations are the most frequent (20-30%). *CD46* mutations are found in approximately 5-15% and *CFI* mutation in in approximately 4-10%. Mutations in components of the coagulation pathway (e.g., thrombomodulin, diacylglycerol kinase ε, and plasminogen) can cause modulation of complement activation (see TMA-coagulation mediated fact sheet) and account for ~5% of cases. Variants in *CFHR1* genes are associated with acquired complement dysregulation due to factor H autoantibodies (FHAA). FHAA occurs in 5-13% of patients. A mutation is not identified in ~20-30%. Penetrance of genetic forms is ~50%. Complement activating conditions, such as infection, pregnancy, autoimmune disease, transplantation, or drugs, may trigger clinical disease in presence of these mutations. A history of recurrent infections from *Streptococcus* or other encapsulated microorganisms such as *Neisseria meningitidis* or *Haemophilus influenza* should suggest a familial etiology. Diagnosis relies on 1) lack of associated disease, 2) no criteria for Shiga-toxin HUS, i.e., negative stool culture and PCR for Shiga toxin, and 3) no criteria for thrombotic thrombocytopenic purpura (TTP; i.e., ADAMTS13 activity >10%).

Current management/treatment

Eculizumab, a humanized anti-C5 monoclonal antibody, blocks activation of the terminal complement cascade, inhibiting complement-mediated TMA. Eculizumab is effective in patients with and without identified genetic mutations and is recommended by several guidelines as the front-line therapy for aHUS. Empiric plasma therapy, either as TPE or plasma infusion (TPE/PI), is recommended while investigations for TTP and other forms of TMA are in progress or if eculizumab is not available. Once other causes of TMA have been excluded, eculizumab should be initiated. A retrospective study of 31 adults observed better outcomes in patients treated with eculizumab and TPE/PI compared to those treated with TPE/PI alone (Cao, 2018). Rituximab and other immunosuppressive therapies may also be initiated in combination with TPE, particularly in FHAA. The data on the use of eculizumab in FHAA is limited albeit promising. Kidney transplantation risks recurrence of the disease process in the allograft. The risk of recurrence is low with MCP but high for *CFH*, *CFI*, and *C3* types of aHUS. Liver transplant may be a curative therapy.

Rationale for therapeutic apheresis

TPE removes the autoantibody or mutated circulating complement regulators while replacing absent or defective complement regulators. In the eculizumab era, the role of TPE in aHUS is becoming more limited. A review of CRs of aHUS published from 2005-2015, observed the mortality rate decreased with eculizumab, but did not change with TPE versus non-TPE groups (Krishnappa, 2018). Retrospective analysis of pregnancy associated aHUS (56% of patients with complement gene abnormalities) found no difference in ESRD and chronic kidney disease in patients who received TPE versus those who did not (Bruel, 2017). However, before a diagnosis of aHUS is confirmed, standard of care is to initiate TPE when TTP is suspected. When eculizumab is not available, TPE/PI remains an alternative treatment option, although the evidence suggests a more robust effect with eculizumab. Despite weak evidence, TPE is recommended as first line therapy for FHAA due to effective removal of circulating antibodies by TPE; the combination of TPE and immunosuppression for antibody reduction has been effective. A specific recommendation for MCP (*CD46*) has been removed as the factor does not circulate and TPE has not been shown to influence outcomes. Plasma infusions can be considered in patients for whom eculizumab and TPE are not available. A multicenter study did not observe differences in remission rates when patients were treated with plasma infusions versus TPE (Noris, 2010).

Technical notes

As many affected patients are children, establishment of vascular access, circuit priming, and calcium supplementation are of special concern. Use of solvent-detergent plasma as the replacement fluid of TPE has been reported.

Volume treated: 1-1.5 TPV	**Frequency:** Daily
Replacement fluid: Plasma or Plasma/Albumin	

Duration and discontinuation/number of procedures

As there is no standardized approach, the duration and schedule of TPE for treatment of TTP have been empirically adopted. Duration or discontinuation of TPE should be based upon patient condition and response. When TPE is started before a diagnosis is established, it is important to obtain relevant laboratory testing such as PCR for Shiga toxin, ADAMTS13, and anti-factor H.

Key words: atypical hemolytic syndrome, complement-mediated thrombotic microangiopathy, plasma exchange, thrombotic microangiopathy, complement

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THROMBOTIC MICROANGIOPATHY, DRUG ASSOCIATED

Incidence: Ticlopidine/Clopidogrel: <1%; Gemcitabine: <1%; Quinine: rare	**Indication**	**Procedure**	**Recommendation**	**Category**
	Ticlopidine	TPE	Grade 2B	I
	Clopidogrel	TPE	Grade 2B	III
	Gemcitabine/Quinine	TPE	Grade 2C	IV
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Ticlopidine/Clopidogrel	0	0	5(174)	NA
Gemcitabine	0	0	3(39)	16(18)
Quinine	0	0	3(32)	8(8)

Description of the disease

Drug induced thrombotic microangiopathy (DI-TMA) is characterized by the development of TMA (syndrome consisting of microangiopathic hemolytic anemia, thrombocytopenia, and microvascular thrombosis) in association with exposure to a drug. Contemporary review articles utilize the general term DI-TMA to describe patients previously referred to as having both drug-induced hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). While several drugs have been reported, the most commonly implicated include: clopidogrel, calcineurin inhibitors (CNIs), estrogen/progesterone, gemcitabine, interferon, mitomycin, quinine, and ticlopidine. Recent CRs have also implicated oxymorphone, bevacizumab, carfilzomib, ixazomib, and palbociclib. In addition, herbal remedies and illicit drugs are also known to have the potential to cause DI-TMA. Please refer to the TMA, transplantation associated fact sheet for discussion of CNI-induced TMA.

Current management/treatment

Initial management involves immediate discontinuation of suspected drug, or reduction of dose when discontinuation is not a therapeutic option. Supportive care and other interventions reported for specific drugs include gemcitabine: dialysis, antihypertensives, corticosteroids, rituximab; quinine: corticosteroids, antiplatelet agents; bevacizumab: steroids, cyclophosphamide; cyclosporine/tacrolimus/sirolimus: use of alternate immunosuppression (see separate fact sheet). Eculizumab, a C5 inhibitor approved for the treatment of paroxysmal nocturnal hemoglobinuria and atypical HUS, has been utilized in the setting of DI-TMA with success, even in patients in whom TPE has failed. The largest CS in which eculizumab was compared with conventional therapy found that in patients with DI-TMA following allogeneic HSCT fared better with the use of eculizumab than TPE (Bohl, 2017). The use of TPE should be individualized per patient, depending on the mechanism of toxicity leading to the DI-TMA, especially with the availability and apparent efficacy of eculizumab. Of course, when TTP is clinically suspected, directed treatment including TPE should be undertaken while waiting for confirmatory diagnosis (see separate fact sheet).

Rationale for therapeutic apheresis

The use of TPE is based on extrapolation of its effectiveness for idiopathic TTP. However, unlike idiopathic TTP, drug associated TMA is rarely associated with severe deficiency of ADAMTS13 levels or presence of inhibitors (exception noted below). Pathogenesis is multifactorial including autoimmunity, drug-dependent antibodies and endothelial toxicity. Other causative factors include presence and progression of pre-existing medical conditions such as malignancy, AKI, or hypertension. Therefore, therapeutic rationale for TPE is unclear, which is reflected in reported heterogeneous clinical results.

Two potential mechanisms for DI-TMA have been proposed, immune-mediated reactions and dose or duration related toxicity; either may result ultimately in renal failure. A detailed review of some of the most common causative drugs and the mechanisms by which they cause DI-TMA provides rationale as to why TPE may not be effective (Kreuter, 2012).

Specific drug information as it relates to TPE use: Ticlopidine: ADAMTS13 levels are typically severely diminished (<10%) with inhibitors present. Most patients develop TMA >2 weeks after initial drug exposure with most cases responding to TPE. Clopidogrel: ADAMTS13 levels are typically normal. Patients usually present ≤2 week of starting therapy. Most cases have mild hematologic and marked kidney involvement. The majority are unresponsive to TPE. Gemcitabine: ADAMTS13 levels are typically normal. In a literature review, among 26 patients not treated with TPE, 56% recovered from TMA, compared to 30% of 18 patients who received TPE (Glezerman, 2009). However, the group receiving TPE appeared to be more severely ill and more likely to have received dialysis. Quinine: A CS of 19 patients with quinine-induced TMA from the Oklahoma TTP/HUS Registry were treated with TPE due to an initial concern for TTP had disappointing results. Seventeen required dialysis and 14 went on to develop chronic kidney disease; 9 patients died (Page, 2017).

Technical notes

Data regarding replacement fluid and frequency of TPE are limited. Similar procedural considerations apply as with TPE for TTP, however laboratory parameters and clinical response may be variable.

Volume treated: 1-1.5 TPV	**Frequency:** Daily or every other day
Replacement fluid: Plasma	

Duration and discontinuation/number of procedures

Performed daily until recovery of hematologic parameters and then either discontinued or tapered off, similar to treatment for idiopathic TTP.

Keywords: Drug induced thrombotic microangiopathy, plasma exchange, quinine, gemcitabine, bevacizumab, ticlopidine, clopidogrel, cyclosporine, tacrolimus, sirolimus, calcineurin inhibitors, mitomycin

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THROMBOTIC MICROANGIOPATHY, INFECTION ASSOCIATED

Incidence: STEC-HUS: <2/100,000; pHUS: <1%	**Indication**	**Procedure**	**Recommendation**	**Category**
	STEC-HUS, severe	TPE/IA	Grade 2C	III
	pHUS	TPE	Grade 2C	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
STEC-HUS	1(35)	1(37)	>50	NA
pHUS	0	0	2(12)	3(3)

STEC-HUS = thrombotic microangiopathy, shiga toxin-mediated; pHUS = thrombotic microangiopathy due to *Streptococcus pneumoniae*

Description of disease

Hemolytic uremic syndrome (HUS), is a potentially life-threatening condition characterized by TMA that typically targets the kidney causing renal failure. In 90% of patients with HUS, the cause is due to the action of Shiga-like toxin (Stx) on the renovascular endothelium and is often referred to as STEC-HUS (D+HUS). STEC-HUS occurs most frequently in younger children, and 2-10 days after a prodrome of bloody diarrhea due to verocytotoxin (Stx)-producing bacteria, predominantly *E. coli* O157:H7. Outbreaks and sporadic cases linked to other *E. coli* serotypes, *Shigella dysenteriae*, or other microorganisms producing Stx continue to be reported. STEC enteritis usually leads to HUS in 5-15% of cases. In 2011, Europe experienced one of the largest recorded STEC-HUS outbreaks. A total of 3,842 people were affected by a virulent and uncommon strain of enteroaggregative hemorrhagic *E. coli* (EAHEC) O104:H4. HUS developed in 855 (80% adults) with 54 deaths reported. Stx have proinflammatory and prothrombotic effects on the vascular endothelium and may attach to and stimulate endothelial cells to release "unusually large" von Willebrand factor multimers (ULVFWM) which activate and promote adhesion and aggregation of platelets. Stx binds to multiple cells in the kidney and causes a spectrum of renal injury, including vascular endothelial cell damage, thrombotic occlusion of the capillary lumen, glomerular endothelial cell swelling, apoptosis of glomerular and tubular cell, and extensive cortical necrosis in the kidneys. About a third of cases will require dialysis. Recurrent kidney injury may occur. Brain endothelial and neuronal cells are also targeted. The severity of acute illness, particularly central nervous system impairment and the need for dialysis is strongly associated with a worse long-term prognosis. Mortality is between 1-5% but up to 30% of patients may have long term complications including; hypertension, end stage renal disease requiring renal transplantation, diabetes and neurological symptoms.

Another infection-induced HUS that usually occurs in children <2 yr is due to sepsis, pneumonia, or meningitis caused by *Streptococcus pneumoniae* (pHUS). It has a mortality of 19-50%. *S. pneumoniae*, as well as other bacteria and viruses, produce a neuramidase which cleaves sialic acid residues from cell surface glycoprotein exposing the Thomsen-Freidenreich (T-) antigen. pHUS may occur by binding of naturally occurring IgM anti-T antibody to exposed T-antigen on erythrocytes, platelets and endothelium. Mortality rates are as high as 50%.

Current management/treatment

Supportive care is the mainstay of therapy including fluid management, treatment of hypertension and renal replacement therapy. There is no evidence of any benefit of glucocorticoid therapy. There is no compelling evidence from the available literature that TPE benefits patients with STEC-HUS, although patients with severe bloody diarrhea or neurological involvement may respond to timely TPE. In the 2011 outbreak in Germany, TPE was performed in 251 patients yet evidence of benefit was not seen (Menne, 2012). However, in the same outbreak, TPE appeared to ameliorate the course in 5 adults treated in Denmark, with acute kidney injury and central nervous system dysfunction (Colic, 2011). In the same outbreak in Germany, IA was safely used to rapidly ameliorate severe neurological deficits in a prospective trial of 12 patients unresponsive to TPE or eculizumab (Greinacher, 2011). Previously a retrospective study from France had identified acute neurological involvement in STEC-HUS, half of whom responded to TPE suggesting some benefit in this specific clinical setting (Nathanson, 2010).

Stx has been shown in vitro and in vivo to activate the alternative complement pathway. A French group found no difference in patient outcome with the use of eculizumab, however, suggested that as potentially more severely ill patients were treated with eculizumab, and that they still showed a comparable outcome to untreated patients (Percheron, 2018). Different regimens (TPE, plasma infusion, IA, eculizumab), many times in escalating manner, continue to be used for patients with renal symptoms only or extrarenal complications, especially neurological. One group found elevated level of sC5b-p as a predictor for poor outcome, but not as a clear parameter for a treatment decision.

Rationale for therapeutic apheresis

TPE may reduce concentrations of various cytokines, ULVWFM and Stx that damage the endothelium, however, there is limited data to support this. Free Stx has not been detected in the serum, and how it transits from the GI tract to target organs remains unclear. For pHUS, TPE would remove antibodies directed against the exposed T-antigen, as well as circulating bacterial neuraminidase. Experience with TPE for pHUS is limited without reported adverse effects.

Technical notes

When TPE is performed in children with pHUS, avoidance of plasma-containing blood components is recommended to prevent the passive transfer of anti-T in normal plasma and possible polyagglutination due to T-activation.

Volume treated: 1-1.5 TPV	**Frequency:** Daily
Replacement fluid: STEC-HUS: Plasma; pHUS: Albumin	

Duration and discontinuation/number of procedures

No standardized approach, the duration and schedule of TPE for treatment of TTP have been empirically adopted to treat HUS. Decisions of duration or to discontinue should be made based upon patient response and condition.

Keywords: hemolytic uremic syndrome, thrombotic microangiopathy, shiga toxin, *Streptococcus pneumoniae*, plasma exchange

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THROMBOTIC MICROANGIOPATHY, THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

Incidence: <1/100,000/yr		**Procedure**	**Recommendation**	**Category**
		TPE	Grade 1A	I
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	7(301)	5(270)	NA	NA

Description of the disease

Thrombotic thrombocytopenic purpura (TTP), is a systemic thrombotic illness affecting mostly small vessels. It was originally defined by the pentad of severe thrombocytopenia, microangiopathic hemolytic anemia (MAHA), mental status changes, renal failure and fever. However, clinical findings of unexplained thrombocytopenia and MAHA are enough to make a presumptive diagnosis of TTP. Because TTP is potentially fatal if left untreated (~90% mortality), there should be a low threshold to treat presumed TTP. Treatment is usually initiated urgently within 4-8 hours of diagnostic suspicion, after other causes of systemic TMA have been considered unlikely. TTP is associated with a severe (<10%) deficiency of plasma ADAMTS13 enzyme activity, which is responsible for maintaining normal distribution of von Willebrand factor (vWF) multimers. The PLASMIC scoring system has been developed to predict severe ADAMTS13 deficiency and includes 5 independent variables identified as highly predictive by multivariable regression including platelet count $<30 \times 10^9$/L, creatinine <2.0 mg/dL, INR <1.5, MCV <90 fL, and hemolysis. The PLASMIC scoring system has been validated in two different cohorts and when used in conjunction with clinical evaluation may help to quickly diagnose new TTP patients (Bendapudi, 2017).

Congenital TTP comprises a minority of cases and is associated with somatic mutations resulting in severely deficient ADAMTS13 function. Most patients have immune mediated TTP where autoantibody against ADAMTS13 is detected. IgG4 is the most common anti-ADAMTS13 IgG subclass and appears to be related to disease recurrence.

Current management/treatment

TPE has decreased overall mortality of immune mediated TTP from nearly uniformly fatal to <10-20%. TPE should be initiated emergently once the diagnosis is recognized. If TPE is not immediately available, large dose plasma infusions (25-30 mL/kg), may be given if tolerated, until TPE can be initiated (Coppo, 2003). Corticosteroids should be used as an adjunct, either a daily prednisone dose at 1 mg/kg/day, pulsed methylprednisone for a few days, or a combination; however, no definitive trials proving their comparative efficacy have been performed. Rituximab is commonly used to treat refractory or relapsing TTP. Studies have also described the incorporation of rituximab as adjunctive agent with initial TPE. Since rituximab immediately binds to CD20-bearing lymphocytes, an 18-24-hour interval between its infusion and TPE is used in practice. Other adjuncts for refractory or relapsing TTP include cyclosporine, azathioprine, vincristine, bortezomib and other immunosuppressive agents. Splenectomy has been used in the past and may be considered for severe refractory cases. Caplacizumab is an anti-vWF nanobody directed against the platelet binding domain (A1) of vWF. When added to TPE plus immunosuppression in a phase II placebo-controlled RCT it induced a significantly faster resolution of acute TTP episode (Peyvandi, 2016). HERCULES, a phase III randomized, double-blind, placebo-controlled study demonstrated that patients with acquired TTP receiving caplacizumab were 1.5x more likely to normalize platelet count and had a 74% lower risk of a composite of TTP-related death, recurrence, or a major thromboembolic event while undergoing treatment compared to those patients receiving placebo (Scully, 2019). Other promising agents under evaluation include N-acetylcysteine and recombinant ADAMTS13.

Patients with TTP have a thrombotic rather than hemorrhagic tendency and bleeding, if present, is typically limited to skin and mucous membranes. Platelets should only be transfused if potential life-threatening bleeding is present. Because congenital TTP is characterized by constitutive deficiency of ADAMTS13 activity without an inhibitor, simple infusions of plasma (10-15 mL/kg) or cryoprecipitate (which contains ADAMTS13) or plasma derived vWF concentrates have been used.

Rationale for therapeutic apheresis

TPE with plasma replacement has significantly improved patients' clinical outcomes. One hypothesis is that TPE removes anti-ADAMTS13 autoantibody, while replacing ADAMTS 13 protease activity. However, clinical course does not always correlate with plasma ADAMTS13 activity or ADAMTS13 inhibitor levels.

Technical notes

Allergic reactions and citrate reactions are more frequent due to large volumes of plasma required. Since plasma has citrate as an anticoagulant, ACD-A can be used in a higher ratio (to whole blood) to minimize citrate reactions. Fibrinogen levels may decrease following serial TPE procedures with cryoprecipitate depleted plasma as replacement. A previous study demonstrated that that the use of cryoprecipitate depleted plasma as replacement may be associated with more frequent acute exacerbations (Stefanello, 2014). Solvent detergent treated plasma may be used for patients with severe allergic reactions. In addition, combined use of 50% albumin and 50% plasma has been reported to result in similar treatment efficacy as compared to the replacement of 100% plasma with albumin being used for the initial portion (up to 50%) of replacement (O'Brien, 2013).

Volume treated: 1-1.5 TPV	**Frequency:** Daily
Replacement fluid: Plasma or Plasma/Albumin	

Duration and discontinuation/number of procedures

TPE is generally performed daily until the platelet count is $>150 \times 10^9$/L, and LDH is near normal for 2-3 consecutive days. The role of tapering TPE over longer duration has not previously been studied prospectively but is currently being reviewed. A small retrospective study suggests a lower overall recurrence rate at 6 months with taper. A common taper strategy is three times a week for the first week, twice weekly the second and then once weekly the following week(s). Other taper approaches have been documented.

Keywords: Thrombotic thrombocytopenic purpura, thrombotic microangiopathy, plasma exchange

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THROMBOTIC MICROANGIOPATHY, TRANSPLANTATION ASSOCIATED

Incidence: 10-40% in allogeneic HSCT		**Procedure**	**Recommendation**	**Category**
		TPE	Grade 2C	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Post-HSCT	0	0	29(416)	NA

HSCT = hematopoietic stem cell transplantation

Description of the disease

Thrombotic microangiopathy (TMA) following hematopoietic stem cell transplantation (HSCT), also referred to as transplant associated TMA (TA-TMA), is a potentially severe complication of HSCT. TA-TMA appears to be primarily triggered by mechanisms of endothelial cell injury, including high-dose conditioning chemotherapy, irradiation, graft-versus-host disease (GVHD), mTOR and calcineurin inhibitor drugs (used to prevent and treat GVHD), and infections. Damaged and apoptotic endothelial cells generate inflammatory cytokines, microparticles, release of von Willebrand factor (vWF) and induce platelet adhesion/aggregation and a procoagulant state. Unlike idiopathic thrombotic thrombocytopenic purpura (TTP), plasma ADAMTS13 protease level is not severely deficient nor is ADAMTS13 inhibitor activity detectable. Over the last decade, studies suggest there may be involvement of complement dysregulation. The incidence of TA-TMA is 10-40% in allogenic HSCT patients. The endothelial injury affects multiple organs. Kidneys are the major target organs affected, but the central nervous system, pulmonary, gastrointestinal and serosa may also be affected. Diagnosis can be made histologically; however, in patients following HSCT, this is not always feasible and clinical and laboratory criteria are relied upon. These include microangiopathic hemolytic anemia with high lactate dehydrogenase (LDH) and low haptoglobin, thrombocytopenia, schistocytes on the blood smear, hypertension, and proteinuria. Noninvasive diagnostic criteria for TA-TMA include evidence of terminal complement activation with an elevated plasma concentration of sC5b-9. A high index of suspicion is needed as anemia, thrombocytopenia, and increased creatinine are not uncommon post-HSCT. In patients with elevated LDH, proteinuria and hypertension, a diagnosis of TA-TMA should be strongly considered. TMA can occur within the first few weeks following transplant or as a late complication (up to 8 months). TA-TMA carries a poor prognosis. The mortality rates in patients who develop severe TA-TMA is >80%.

Current management/treatment

Initial management is mostly supportive and includes tight control of blood pressure, treatment of co-existing infections, and management of GVHD. Reduction or discontinuation of mTOR and calcineurin inhibitor drugs is commonly performed in the setting of TA-TMA; however, there is no evidence to support this practice in the face of active GVHD, and decisions to discontinue or change immunosuppression must be made on an individual basis. With increasing data becoming available regarding the involvement of complement dysregulation in some patients with TA-TMA, the complement-inhibiting monoclonal antibody eculizumab has been used with some success. However, one study compared TA-TMA patients having received eculizumab to historical patients receiving conventional therapy and despite a very good response in the eculizumab-treated group, there was no significant improvement in overall survival, due primarily to a high rate (70%) of infection-related mortality (Bohl, 2017). Other treatment options include rituximab, defibrotide, IL-2 receptor antibodies, pravastatin, and TPE.

No RCTs have addressed the efficacy of TPE for TA-TMA. CSs have reported overall response rates with TPE (usually after drug withdrawal) ranging from 0-72%, but with frequent partial responses, relapses and up to 15% procedural adverse events. In addition, patients often receive multiple treatments which limits the ability to separate out clearly the effect of TPE. Despite the poor efficacy of TPE overall, patients who present with TA-TMA more than 100 days after HSCT may have better outcome and lower mortality (Mulay, 2015).

A single center observational study of 63 patients observed TPE responses only among those who also responded to treatment of GVHD and/or infections, suggesting that TPE alone does not reverse the TMA pathophysiology (Oran, 2007). A systematic review of published reports noted an 82% mortality rate among 176 patients with TA-TMA who underwent TPE compared to 50% mortality among 101 patients not treated with TPE (George, 2004). Similarly, high cumulative mortality rates were cited by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Toxicity Committee, and in a consensus statement recommended that TPE not be considered as a standard of care for HSCT-TMA (Ho, 2005). In children with TA-TMA there is some evidence that very early initiation of TPE might be beneficial, even in patients with multiorgan failure.

Rationale for therapeutic apheresis

The use of TPE is based on extrapolation of its effectiveness for idiopathic TTP. However, numerous studies have confirmed that plasma ADAMTS13 protease levels are not severely deficient nor are ADAMTS13 inhibitors detectable in patients with TA-TMA. Therefore, therapeutic rationale is undefined and consistent with the uncertain clinical efficacy. A retrospective study in 15 patients demonstrated that treatment with at least 7 weeks of TPE did not prevent the development of chronic kidney disease in TA-TMA patients (Sartain, 2018). Because some patients appear to respond to TPE, a trial could be considered as salvage therapy for select patients with persistent or progressive TA-TMA despite resolution of infections and GVHD.

TMA can also be a rare but serious complication following solid organ transplant and may be associated with calcineurin inhibitor and mTOR inhibitor use. It is associated with a high degree of morbidity or mortality and can result in loss of the graft. The value of TPE following solid organ transplant remains controversial (Verbiest, 2014).

Technical notes

TPE for patients with TA-TMA is often complicated by thrombocytopenia, anemia and co-morbidities related to GVHD and infections, including bleeding and hypotension. Therefore, the pattern of platelet and LDH responses may be variable and incomplete compared to patients undergoing TPE for idiopathic TTP. This may make a therapeutic endpoint difficult to determine. ACD-A should be used as anticoagulant in patients with bleeding risk.

Volume treated: 1-1.5 TPV **Frequency:** Daily, or as indicated for chronic management

Replacement fluid: Plasma or Plasma/Albumin

Duration and discontinuation/number of procedures

TPE is usually performed daily until a clinical response is achieved and then either discontinued or tapered off, similar to treatment for idiopathic TTP.

Keywords: thrombotic microangiopathy, hematopoietic stem cell transplantation, transplantation-associated thrombotic microangiopathy, plasma exchange

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THYROID STORM

Prevalence: 1/100,000		**Procedure**	**Recommendation**	**Category**
		TPE	Grade 2C	II
# reported patients: 100-300	**RCT**	**CT**	**CS**	**CR**
	0	0	15(133)	NA

Description of the disease

Hyperthyroidism is characterized by increased thyroid hormone synthesis and secretion from the thyroid gland, whereas thyrotoxicosis refers to the clinical syndrome of excess circulating thyroid hormones, irrespective of the source. Thyroid storm is an extreme manifestation of thyrotoxicosis. This uncommon but serious complication occurs mostly in patients with Graves' disease and less often in toxic multinodular goiter, or solitary toxic adenoma. The cause of Graves' disease is thought to be multifactorial, arising from the loss of immunotolerance and the development of autoantibodies that stimulate thyroid follicular cells by binding to the TSH receptor. The exact mechanism underlying the subsequent development of thyroid storm from uncomplicated hyperthyroidism is not well understood. A common hypothesis for this condition is the presence of both larger availability of adrenergic receptors and a reduction of thyroid hormone binding to thyroid hormone binding globulin (TBG); these result in leaking catecholamines to precipitate thyroid storm.

Thyroid storm is an emergency with a mortality rate up to 25%. Symptoms are usually, but not always, precipitated by infection (most common cause in the inpatient setting), trauma, surgical emergencies, withdrawal of anti-thyroid medications, operations (particularly thyroidectomy), radiation thyroiditis, diabetic ketoacidosis, severe emotional stress, cerebrovascular disease, use of tyrosine-kinase inhibitors, toxemia of pregnancy, or parturition. Amiodarone-induced thyroid storm is more prevalent in iodine-deficient geographic areas. Patients with preexisting hyperthyroidism that had been partially or untreated are also at higher risk. The clinical picture is one of severe hypermetabolism and systemic decompensation (e.g., fever, tachycardia and arrhythmias, heart failure, tremulousness and restlessness, delirium or frank psychosis, nausea, vomiting, and abdominal pain, and, as the disorder progresses, apathy, stupor, and coma, hypotension, and multi-organ failure). Hence, this clinical picture in a patient with a history of preexisting thyrotoxicosis, with goiter or exophthalmos, is sufficient to establish the diagnosis. Burch and Wartofsky created a scoring system to help standardize its diagnosis using body temperature, central nervous system involvement, gastrointestinal-hepatic dysfunction, heart rate, and the presence or absence of congestive heart failure and/or atrial fibrillation. When a clinical diagnosis is made, emergency treatment should be initiated prior to laboratory confirmation. Serum T_3 or T_4 concentration cannot differentiate between severe thyrotoxicosis and thyroid storm.

Current management/treatment

A multimodality treatment approach is highly recommended, which includes medications stopping the thyroid hormone synthesis (propylthiouracil [PTU] as preferred antithyroid drug) and release (iodine), blocking T_4 to T_3 conversion (glucocorticoids), inhibiting the enterohepatic circulation of thyroid hormone (cholestyramine), controlling the peripheral effects of the thyroid hormones (ß-blockers), managing high fever, and overall hemodynamic stabilization. If a precipitating event is present, then it should also be treated concurrently. The order of treatment is important. PTU should be started before iodine in order to prevent stimulation of more thyroid hormone synthesis. Depending on clinical status, the two agents may be administered as close as 30-60 minutes apart. Controlling the cardiovascular manifestations of thyroid storm is vital, large doses of ß-blockers might be required. Aspirin or other salicylates should not be used because they increase serum hormone levels.

Rationale for therapeutic apheresis

Both TPE and emergency surgery have been used to treat thyroid storm in patients who respond poorly to first line therapeutic measures. TPE is usually performed in patients with thyroid storm with severe symptoms and when the patient does not improve with first-line therapies within 24-48 hours of treatment or when first-line therapies cannot be used due to toxicity, such as leukopenia due to PTU. Since a portion of T_3 and T_4 is firmly bound to plasma proteins, TPE should, in theory, efficiently reduce their circulating pool and as such, most patients had a decrease in the hormone concentrations. In a review of the literature, TPE decreased the levels of free T4 and T3, and total T3 and T4 significantly (Garla, 2018). In patients with amiodarone-associated thyrotoxicosis, TPE has also been used to reduce the amiodarone plasma concentration, which has a half-life of months in patients on chronic therapy. TPE in this condition is particularly indicated for patients who have no underlying thyroid disease and develop a drug-induced destructive thyroiditis. The therapeutic benefit of TPE can be achieved by removal of potential substances from the thyroid storm such as autoantibodies (Graves' disease), catecholamines (released by the sympathetic system) and cytokines. In rare cases, TPE is used to render the thyrotoxocotic patient euthyroid prior to thyroidectomy. TPE effect is transient and the hormone levels typically rise again the next day. Continuous dialysis modalities, e.g,. with albumin containing dialysate, were experimentally used to increase thyroid hormone clearance. If removal of autoantibodies is considered for stabilizing the therapeutic result, in particular with associated ophthalmopathy, selective apheresis methods like IA or DFPP have been used.

Technical notes

Plasma as replacement fluid has the advantage of increasing the concentration of TBG to bind free thyroid hormone. However, albumin provides a larger capacity for low-affinity binding of thyroid hormones and thus, decreasing the free thyroid hormone concentration.

Volume treated: 1-1.5 TPV	**Frequency:** Daily to every 3 days guided by control of systemic symptoms.
Replacement fluid: Plasma, albumin	

Duration and discontinuation/number of procedures

TPE should be continued until clinical improvement is noted. Usually 3-6 procedures are performed to achieve clinical stabilization.

Keywords: Hyperthyroidism, plasma exchange, plasmapheresis, thyroid storm, thyrotoxicosis

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TOXIC EPIDERMAL NECROLYSIS (TEN)

Incidence: 2/1,000,000/yr	**Indication**	**Procedure**	**Recommendation**	**Category**
	Refractory	TPE	Grade 2B	III
# reported patients: 100-300	**RCT**	**CT**	**CS**	**CR**
	0	0	15(172)	NA

Description of the disease

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), also called Lyell syndrome, represent a spectrum of severe idiosyncratic reactions with medications being the most common trigger. They are characterized by mucocutaneous lesions leading to necrosis and sloughing of the epidermis. Classification of SJS and TEN is determined mainly by severity and percentage of body surface involved. SJS is the less severe condition, in which skin sloughing is limited to <10% of body surface area (BSA) while mucous membranes are affected in >90% of patients. TEN involves sloughing of >30% BSA with nearly 100% involvement of mucous membranes. In SJS/TEN overlap syndrome, patients have BSA involvement of >10% but <30%. Exposure to the inciting drug commonly precedes the onset of symptoms by 1-3 weeks in medication-related cases. Upon re-exposure, symptoms may recur in as little as 48 hours. Typically, there is a prodrome of fever and flu-like symptoms. In the early stages of the disease, skin pain may be prominent and out of proportion to clinical findings. Skin lesion distribution is symmetrical, starting on the face and chest before spreading to other areas. Vesicles and bullae form followed, usually within days, by skin sloughing. Prognosis is related to the extent of epidermal involvement. Re-epithelialization typically occurs with 1-3 weeks. Fulminant cases of TEN highly resistant to therapy have been described. Skin biopsy in TEN shows full thickness epidermal necrosis, subepidermal detachment and mild lymphocytic infiltration at the dermoepidermal junction. Mortality in SJS is 1-3%, while mortality for TEN is 25-30%. The pathogenesis of SJS/TEN remains incompletely understood. Proposed mechanisms implicate granulysin (a protein secreted by cytotoxic T and NK cells), fas/fas-ligand mediated keratinocyte apoptosis, perforin, reactive-oxygen species, and TNF-alpha in mediating keratinocyte cell death. There is a strong associated between the HLA-B*1502 allele and carbamazepine induced TEN.

Current management/treatment

For medication-induced SJS/TEN, the causative mediation is immediately withdrawn. Delayed removal of the causative drug and drugs with long half-lives are associated with worse prognosis. A prognostic scoring system (SCORTEN) based upon easily measured clinical and laboratory variables has been validated for use on days 1 and 3 of hospitalization. TEN is managed by administration of glucocorticoids, cyclosporine, and supportive care in an intensive care unit or burn center, and includes skin care, fluid and electrolyte management, nutritional support, eye care, temperature management, appropriate analgesia, and treatment of infections. Fluid and electrolyte losses may occur due to the extensive mucocutaneous lesions. TEN patients are at high risk for infection, and sepsis is a major cause of death. Aggressive culturing and sterile precautions are important in minimizing this risk. Use of prophylactic antibiotics is not recommended. Beyond supportive care, there are no universally accepted therapies for this disease. A large meta-analysis of 96 studies comprising 3248 patients suggests a promising survival benefit with the use of glucocorticoid and cyclosporine (Zimmerman, 2017). The effectiveness of IVIG, TPE, biologics, and other agents remains uncertain.

Rationale for therapeutic apheresis

The rational supporting TPE in TEN includes removal of drug/drug metabolites, cytokines or other mediators of keratinocyte cytotoxicity. At least one report has demonstrated decreased levels of serum cytokines following TPE (Narita, 2011). TPE is typically not used in patients with SJS although there is rare use of TPE for SJS complicated by hepatic encephalopathy.

Numerous uncontrolled CRs and CS have noted use of TPE in the setting of severe cases of TEN refractory to standard treatment. Given the significant heterogeneity in patient condition at the time of initiation of TPE, the number of TPE treatments utilized, different concurrent medications that these patients were on, and varied disease severity, a rigorous evaluation of TPE efficacy in TEN is challenging. All reports describe application of TPE in combination with other therapies.

Technical notes

While most reports have utilized TPE to treat refractory TEN, some groups from Japan have also used DFPP, which is not available in the US.

Volume treated: 1-1.5 TPV	**Frequency:** Daily or every other day
Replacement fluid: Plasma, albumin	

Duration and discontinuation/number of procedures

The number of TPE treatments varies considerably from 1 to >5 procedures. Discontinuation has been guided by clinical improvement including pain relief, the lack of appearance of new skin/ocular lesions, or evidence of skin healing.

Keywords: Stevens-Johnson syndrome, Toxic epidermal necrolysis, plasma exchange

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TRANSPLANTATION, CARDIAC

Incidence: ~3200 transplants performed per year (US); Cellular rejection: 21-30% in 1st post-transplant yr; Rejection prophylaxis: rare	**Indication**	**Procedure**	**Recommendation**	**Category**
	Cellular/recurrent rejection	ECP	Grade 1B	II
	Rejection prophylaxis	ECP	Grade 2A	II
	Desensitization	TPE	Grade 1C	II
	AMR	TPE	Grade 2C	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
Cellular/recurrent rejection	0	0	4(58)	2(4)
Rejection prophylaxis	1(60)	2(38)	1(2)	NA
Desensitization	0	4(76)	8(124)	NA
AMR	0	0	>10(>200)	NA

AMR = Antibody mediated rejection

Description of the disease

Cardiac transplantation remains the gold standard for treatment of advanced heart failure refractory to medical therapies. Significant advances in the field of solid organ transplantation, including the intensification of immunosuppression (IS), have significantly enhanced survival and quality of life for cardiac transplant patients. However, increase in IS leads to increased risks including opportunistic infections, secondary malignancies, metabolic derangements, and end organ damage. Unfortunately, despite increased IS therapy, episodes of allograft rejection continue to threaten long-term graft survival; compliance with IS does not alleviate the risk of acute or chronic rejection which may lead to cardiac failure, need for second transplant, or death. Cardiac allograft rejection may be hyperacute (in cases of ABO or major HLA incompatibility), acute antibody medicated (AMR), acute cellular rejection (ACR) (most commonly), or chronic rejection (allograft vasculopathy). ACR is mediated through T cells, while AMR is mediated by antibodies directed against the allograft. Patients experiencing AMR are more likely to experience hemodynamic instability, due to decreased cardiac function. AMR has a poorer prognosis than ACR and is associated with the early development of allograft vasculopathy. Young age, female gender, history of congenital heart disease, high titer of HLA antibodies, positive pre-transplant crossmatch, sensitization to OKT3, or prior cytomegalovirus exposure increases the risk of AMR in these patients.

Current management/treatment

Rejection is treated with immunosuppressive medications. Steroids are often first line therapy; if AMR progresses, rituximab, ECP, and TPE are considered. Desensitization regimens are not well established.

ECP has been shown to improve outcome after recalcitrant/severe rejection following cardiac transplantation. In one large study, ECP treatment in 36 patients decreased rejection significantly (Kirklin, 2006). The hazard for subsequent rejection or death was significantly reduced toward the level of the lower-risk non-ECP treated patients in the study. In an RCT comparing ECP vs non-ECP in the prevention of rejection, the number of episodes of acute rejection per patient was significantly lower in the ECP arm after 6 months (Barr, 1998). However, there was no significant difference in the time to first episode of rejection, incidence of hemodynamic compromise, or survival at 6 and 12 months. In pediatrics, a 20-patient retrospective cohort study found decreased number of rejection episodes in 6 months after ECP compared to 6 months before initiation of therapy (1.5 versus 0.5, $p = 0.002$). Potential markers utilized experimentally to measure response include circulating Tregs, plasmacytoid dendritic cells and cytokine levels.

A consensus conference report on the sensitized patient awaiting heart transplantation discusses several aspects of this process (Colvin, 2015). Several programs treated patients with pre-transplant PRAs >50% with a combination of TPE, IVIG, and rituximab. In a 70-patient retrospective review at a pediatric center, 14 had high PRA and 56 did not (Asante-Korang, 2015). PRA levels were significantly decreased following desensitization protocol including TPE, IVIG, cyclophosphamide, and rituximab. Overall mortality and rejection episodes were decreased in the high PRA group, presumably due to this aggressive desentization approach.

All studies utilizing TPE for AMR have been observational and retrospective in nature. The identification of pathogenic donor specific HLA antibodies includes use of the C1q assay to detect a subset of IgG antibodies capable of fixing complement and may be more specific.

Rationale for therapeutic apheresis

Highly sensitized patients in need of cardiac transplantation face challenges in obtaining a compatible allograft. Apheresis techniques in combination with IS have been tested in desensitization and rejection protocols. ECP reduces production of effector T-cells while expanding Tregs. Tregs (CD4+/CD25+/Foxp3+) suppress the immune system in an antigen-specific fashion; plasmacytoid (tolerogenic) dendritic cells are also induced. ECP does not appear to increase infection risk, but in many patients requires placement of a central venous catheter. The goal of TPE is to remove donor-specific antibodies and/or inflammatory mediators implicated in AMR. Thus, while ECP is used on a chronic basis as an immunomodulatory agent, TPE's role is in the acute setting of rejection/desensitization. In most centers, an ECP series consists of 2 procedures on consecutive days.

Technical notes

Volume treated: ECP: Typically, MNCs are obtained from processing 1.5L of whole blood, but the volume processed may vary based on patient weight and HCT. The 2-process method collects and treats MNCs obtained from processing 2 TBV.

Frequency: ECP: one series, weekly or every 2-8 weeks for several months (regimens vary widely); TPE: Daily or every other day

Replacement fluid: ECP: NA; TPE: Albumin, plasma

Duration and discontinuation/number of procedures

There are no clear criteria for discontinuing treatment in ECP. Treatments are typically continued until improvement/stabilization of symptoms are demonstrated. Regarding TPE, improvement in cardiac function, biopsy findings, and donor specific antibody levels are often used to determine timing of discontinuation.

Keywords heart/cardiac transplantation, cellular rejection, humoral rejection, transplant vasculopathy, photopheresis, plasma exchange, desensitization

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TRANSPLANTATION, HEMATOPOIETIC STEM CELL, ABO INCOMPATIBLE

Incidence: 20-50% of allogeneic donor transplants		Indication	Procedure	Recommendation	Category
		Major ABOi HPC(M)	TPE	Grade 1B	II
		Major ABOi HPC(A)	TPE	Grade 2B	II
		Minor ABOi HPC(A)	RBC Exchange	Grade 2C	III
		Major/Minor ABOi → PRCA	TPE	Grade 2C	III
# reported patients: >300		**RCT**	**CT**	**CS**	**CR**
Major ABOi	TPE	0	0	5(491)	NA
Minor ABOi	RBC Exchange	0	0	3(40)	0
Major/Minor ABOi→ PRCA	TPE	0	0	2(7)	22(30)

ABOi = ABO incompatible; HPC(M) = hematopoietic progenitor cell, marrow; HPC(A) = hematopoietic progenitor cell, apheresis; PRCA = pure RBC aplasia

Description of the disease

The HLA and blood group antigens are inherited independently; as such, approximately half of all allo-HSCT's are performed across the ABO group barrier. Three distinct entities are described: major ABO incompatibility, minor ABO incompatibility, and bidirectional incompatibility in which both major and minor mismatches are present. Major ABO incompatibility refers to the presence of natural antibodies (isoagglutinins) in the recipient against the donor's A and/or B blood group antigens, that may cause acute hemolysis of the RBCs present in infused HPC products. HPC products collected by apheresis (HPC(A)) contain a small number of RBCs (2-5% hematocrit) with total RBC volume typically measuring <20 mL and therefore, acute hemolysis is uncommon. By comparison, bone marrow HPC products (HPC(M)) contain 25-35% RBCs leading to a higher risk of acute, clinically significant hemolysis. Acute hemolysis following the infusion of cord blood is rare, as cord blood HPC products are typically washed to remove excessive RBCs either prior to cryopreservation or after thawing. After major ABO incompatible transplant, RBC engraftment may be delayed in up to 20-30% of cases and 8-26% of patients develop pure RBC aplasia (PRCA) due to persistence of isoagglutinins that destroy donor erythroid precursors. Pre-transplant isoagglutinin titers are not always predictive of the development of delayed engraftment or PRCA after major ABO incompatible transplant.

Minor ABO incompatibility refers to the presence of isoagglutinins in the plasma of the donor HPC product against the recipient's A and/or B antigen. These products may induce acute hemolysis of recipient RBCs if the donor isoagglutinin titer is high (i.e., >128) and infused plasma volume exceeds 200 mL (adult recipient). An additional clinically significant risk with minor ABO incompatibility is the development of a delayed, severe and potentially fatal alloimmune hemolysis, termed passenger lymphocyte syndrome (PLS). PLS typically occurs at 7-10 days post HPC infusion and is caused by donor B lymphocytes that mount an antibody response against host A or B antigens.

Current management/treatment

In major ABO incompatibility, acute hemolysis can be avoided by removing RBCs from the HPC product through automated red cell depletion, or by reducing the recipient's isoagglutinin titer. RBC reduction, which may incur loss of HPCs, is based on institutional guidelines, which usually limit the total infusion of fresh donor red cells to 10-40 mL. Recipient isoagglutinin reduction is performed largely by TPE. IA is also available in some countries. In some European centers, isoagglutinin titer reduction may be accomplished by slowly infusing donor-type RBCs to adsorb antibodies in vivo. Post-transplant PRCA in the setting of major ABO incompatibility usually recovers with early withdrawal of immunosuppression (cyclosporine) and supportive transfusion. Persistent cases may respond to exogenous erythropoietin, rituximab, donor lymphocyte infusions, eltrombopag (Busca, 2018), and/or TPE.

In minor ABO incompatible transplants with donor isoagglutinin titer >128 and HPC plasma volume >200 mL, product plasma reduction is performed to prevent recipient hemolysis. Plasma reduction does not reduce the B lymphocyte content of marrow transplantation and does not reduce the incidence of PLS. PLS is unpredictable and managed expectantly with aggressive transfusion support or RBC exchange using group O RBCs pretransplant to reduce the volume of donor incompatible RBCs. PLS has been anecdotally treated with TPE to rapidly reduce isoagglutinin titer.

Rationale for therapeutic apheresis

For major ABO incompatible transplant, TPE to reduce recipient's isoagglutinin titer prior to infusion of the HPA product can be used as an alternative to RBC reduction of the HPC product. TPE may also improve post-transplant PRCA in the setting of a major ABO incompatibile HSCT by removing persistent host isoagglutinins.

For minor ABO incompatible transplantation, prophylactic RBC exchange can effectively reduce the number of host RBCs that would be the target of the PLS. The published experience suggests that a pretransplant residual host RBC population of 35% or less can significantly mitigate delayed hemolysis in high risk patients. Smaller studies, however, have not demonstrate any clear benefit of RBC exchange in reducing hemolysis when performed following infusion of the HPC product.

Technical notes

TPE should be performed before infusion of major ABO incompatible HPC product, using albumin or combination of albumin and plasma compatible with both donor and recipient as replacement fluid. Automated RBC exchange replaces 1-1.5 patient's RBC volume with group O RBCs. RBC exchange to 35% residual host RBCs.

Volume treated: TPE: 1-1.5TPV; RBC exchange:1-1.5 RBC volumes	**Frequency:** TPE: Daily; RBC exchange: Once
Replacement fluid: TPE: Albumin, donor and recipient ABO-compatible plasma; RBC exchange: Group O RBCs	

Duration and discontinuation/number of procedures

For major ABO incompatibility the recommended safety endpoint for TPE is to reduce the recipient's IgM or IgG antibody titers to <16 immediately before HPC product infusion. If there is a delayed red cell recovery or PRCA post-transplant, TPE may be performed.

Keywords: ABO incompatible**,** Passenger lymphocyte syndrome, hematopoietic stem cell transplantation, hematopoietic progenitor cell, pure red cell aplasia, plasma exchange, red blood cell exchange

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TRANSPLANTATION, HEMATOPOIETIC STEM CELL, HLA DESENSITIZATION

Incidence: DSA in 3-24% of allogeneic HSCTs		**Procedure**	**Recommendation**	**Category**
		TPE	Grade 2C	III
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	3(27)	8(12)

DSA = donor-specific antibody (HLA)

Description of the disease

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative treatment for both malignant and non-malignant disorders. A significant number of patients lack an HLA-identical sibling donor, therefore, alternative sources of stem cells including related or unrelated mismatched (including haploidentical) or umbilical cord are being increasingly used. Many transplant candidates will have pre-formed antibodies directed against the donor's class I and/or class II HLA antigens (HLA DSA); the published literature reports an incidence rate of 3-24%. Common exposures include blood product transfusion, pregnancy, and prior organ or allo-HSCT transplantation. It is important to note that methods of testing for HLA DSA vary by laboratory. Clinical studies suggest that the presence of HLA DSA significantly increases the risk of primary engraftment failure.

Current management/treatment

Current strategies are aimed at identifying and defining HLA antibodies present in the recipient once the donor search has been performed, and if possible, to use this information to avoid selection of allogeneic donors with cognate antigens. However, if the donor availability is limited, approaches including the use of TPE, IA, IVIG, rituximab and bortezomib have been utilized to address the issue of elevated HLA DSA. The number of reports with the use of TPE/IA is limited. The largest study of 14 patients used a protocol that included tacrolimus, mycophenolate mofetil, TPE and IVIG, modeled on commonly utilized desensitization protocols commonly used in incompatible renal transplant desensitization (Leffell, 2015). CRs of buffy coat or platelet transfusions from the HSCT donor (expressing DSA-cognate HLA Class I antigens) have been published; such infusions have successfully decreased DSA levels and resulted in donor stem cell engraftment.

Rationale for therapeutic apheresis

Due to the now recognized role of DSA in engraftment failure, elimination/reduction of these antibodies peritransplant may result in improved outcomes. The limited CRs and CS utilizing desensitization (primarily using TPE and another modality such as IVIG, rituximab or bortezomib) suggest that after adequate desensitization, engraftment successfully occurs in most desensitized patients. It is believed that long-term chimerism may induce B cell and T cell tolerance that in turn results in continued decrease in HLA DSA levels contributing to long term durability of these transplants. In the largest CS on desensitization in HSCT candidates with HLA DSA, the desensitization protocol included alternate-day, single volume TPE followed by low dose (100 mg/kg) CMV hyper-immmune IVIG (Leffell, 2015). Treatment also included tacrolimus and mycophenolate mofetil during the desensitization regimen and bortezomib ~3.5 months prior to desensitization. Using this protocol, DSA levels were decreased in all patients treated with a mean reduction in DSA of 64%. Thirteen of the 14 patients' DSA were below levels typically associated with positive flow cytometric crossmatches; all underwent HSCT and engrafted successfully by day +60 post-allo-HSCT. Although it is unclear if the 100% engraftment rate was primarily due to the effective desensitization protocol, this rate compares very favorably with primary engraftment failure rates of 75% in such patients. Additional, larger studies are warranted to fully establish the impact of these desensitization regimens on engraftment in DSA-positive allo-HSCTs.

Technical notes

Volume treated: 1 TPV	**Frequency:** Every other day
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

The estimated number of TPE treatments is based on baseline DSA levels correlated with flow cytometric or complement-dependent cytotoxic crossmatch assays. In the largest CS, TPE was not performed during pre-transplant conditioning or with post-transplant cyclophosphamide but implemented before conditioning with one additional treatment on the day before graft infusion (Gladstone, 2013). Flow crossmatch positive patients received 4-5 treatments and complement-dependent cytotoxic crossmatch positive patients received additional treatments. In addition, patients with DSA rebound may require additional TPE treatments in the post-transplant phase.

Keywords: Hematopoietic stem cell transplantation, desensitization, hematopoietic progenitor cell, graft rejection, plasma exchange

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TRANSPLANTATION, LIVER

Incidence: Rare		**Indication**	**Procedure**	**Recommendation**	**Category**
		Desensitization, ABOi LDLT	TPE	Grade 1C	I
		Desensitization, ABOi DDLT*/AMR**	TPE	Grade 2C	III
		Desensitization, ABOi	ECP	Grade 2C	III
		Acute rejection/Immune suppression withdrawal	ECP	Grade 2B	III
# reported patients: >300		**RCT**	**CT**	**CS**	**CR**
Desensitization: ABOi LDLT	TPE	0	0	15(1230)	NA
Desensitization: ABOi DDLT	TPE	0	0	7(60)	9(9)
Immune suppression withdrawal	ECP	0	3(457)	NA	NA
Desensitization: ABOi	ECP	0	2(31)	0	0

ABOi = ABO-incompatible; LDLT = Living donor liver transplant; DDLT = Deceased donor liver transplant; AMR = Antibody mediated rejection;
*TPE based desensitization is not indicated in the setting of group A-subtype (e.g., A_2) into group O DDLT;
**includes ABOi and HLA DSA

Description of the disease

Liver transplantation can be a life-saving procedure. Apheresis modalities including TPE and ECP can be utilized to desensitize in the setting of ABOi transplantation, prevent/treat biopsy proven rejection, and as substitution for traditional immune suppression. Due to a relative shortage of compatible organs for transplantation and the development of novel methods of immune modulation, ABO incompatible (ABOi) liver transplants are more frequently performed, from both living (segmental) and deceased donors. ABO isoagglutinins may cause hyperacute/acute humoral rejection due to direct, antibody-induced endothelial damage (A and B antigens are expressed on vascular endothelium). Many publications including an expert panel report on the impact of donor specific HLA antibodies on short and long-term outcomes in liver transplantation suggests an additional role of anti-HLA antibodies in mediating liver allograft injury, a mechanism that was previously not thought to be relevant.

Current management/treatment

In the DDLT setting, TPE is typically instituted immediately prior to or both prior to and following transplantation to prevent hyperacute/acute AMR in patients with high anti-A and -B isoagglutinin titers. Since the introduction of rituximab, ABOi LDLT has been increasingly used in East Asia along with TPE, and with or without local hepatic infusion with prostaglandin E1 and methylprednisolone with good survival statistics. As in the ABOi renal transplant setting, rituximab appears to be as effective as splenectomy in enabling ABOi LDLT. Two retrospective studies in 56 and 40 adults, respectively undergoing ABOi living donor liver transplantation received rituximab with or without TPE for desensitization (Lee, 2018; Yamamoto, 2018). In both, there were no differences in survival, rebound anti-blood type isoagglutinin titers or other potential complications, suggesting that rituximab may be sufficient for desensitization. Individuals with the A_2 blood group have reduced expression of the A antigen on endothelium and RBCs; a large retrospective CS of patients undergoing DDLT suggests that A_2 into O transplants is safe with similar graft and overall survival relative to ABO-compatible DDLT, and that additional therapy is not necessary. Humoral rejection due to donor specific HLA antibodies was a controversial entity previously; multiple studies suggest that several liver pathologic conditions including hyperacute rejection, "steroid-resistant" rejection, idiopathic/accelerated fibrosis and biliary strictures, have been associated with HLA donor-specific antibodies.

Rationale for therapeutic apheresis

There are no controlled clinical trials using TPE in ABOi liver transplantation. However, given the significant risks of hyperacute/acute AMR, TPE continues to be used as a key therapeutic modality to reduce anti-A or anti-B isoagglutinin titers in the peri-transplant period. In ABOi LDLT transplantation, TPE is extensively used as part of a desensitization protocol to lower antibody titer below a critical threshold (which differs institutionally based on titration method/technique) prior to the transplant procedure. In DDLT, TPE procedures are often utilized in the urgent/emergent setting after a deceased ABOi allograft has been identified, making a thorough analysis of TPE efficacy challenging. Similarly, TPE has also been used in the setting of AMR in the liver allograft to decease levels of both ABO and HLA antibodies. An increasing number of retrospective studies suggest that TPE, in combination with enhanced immunosuppression may be effective in reversing humoral rejection of the liver allograft. Specific diagnostic criteria to calculate a chronic AMR (cAMR) score has recently been proposed and appears to identify liver allograft recipients at highest risk for allograft loss (O'Leary, 2015). In this indication, TPE is used in conjunction with rituximab, other monoclonal antibodies, and standard immunosuppressive medications such as steroids, a calcineurin inhibitor, and mycophenolate mofetil.

ECP has been utilized in several clinical scenarios in patients following liver transplantation (Mazzoni, 2017). It has been prescribed early in the post-transplant period as prophylaxis against rejection in patients with high risk for calcineurin inhibitor (CNI) induced toxicity, allowing later introduction of traditional immunosuppression. It has also been used in the setting of ABOi liver transplantation with the goal of preventing AMR. Finally, ECP has been used to reduce immune suppression in patients with hepatitis C and biopsy proven acute rejection, along with anti-viral therapy. Treatment schedules for ECP vary among studies.

Technical notes

The replacement fluid for TPE is plasma, or albumin plus plasma (plasma should be compatible with both the recipient and donor organ ABO type in ABOi transplants). Plasma is frequently used in this setting due to underlying coagulopathy secondary to liver failure seen in this patient population. Typical anticoagulation used is ACD-A; heparin-based anticoagulation may be considered if liver function is poor.

ECP can be performed utilizing a commercially available closed system, or with an off-line procedure in which peripheral blood mononuclear cells are collected, and the addition of 8-methoxypsoralen and exposure of cells to UV light are performed in a certified cell therapy facility, then returned to the patient.

Volume treated: TPE: 1 - 1.5 TPV; ECP: In closed system, MNCs collected from processing 1.5L of whole blood but varies depending on patient weight/HCT. The 2-step process collects MNCs from processing 2 TBV

Frequency: TPE: Daily or every other day; ECP: One cycle = two days per week, one cycle weekly or every 2 - 8 weeks for several months (regimens vary widely).

Replacement fluid: TPE: Albumin, plasma; ECP: NA

Duration and discontinuation/number of procedures

The goal of therapy in the setting of ABOi is to reduce the ABO isoagglutinin titer to less than a critical threshold prior to transplant; the threshold of critical titer is center specific. The number of TPE procedures required depends upon the patient's baseline isoagglutinin titer, and on the rate of antibody production/rebound following TPE. For ECP, the duration of therapy varies among studies. Patients should be monitored closely for graft dysfunction before discontinuation of TPE/ECP. For treatment of liver rejection, TPE and ECP are usually used until improvement in liver function (such as liver enzymes, bilirubin, etc).

Keywords: ABO-incompatible liver transplantation, deceased donor liver transplant, living donor liver transplant, liver rejection, liver humoral rejection, antibody mediated rejection, plasma exchange, extracorporeal photopheresis

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TRANSPLANTATION, LUNG

Incidence: BOS: 25% at 3 yr, 50% at 6 yr; AMR: Rare	**Indication**	**Procedure**	**Recommendation**	**Category**
	BOS	ECP	Grade 1C	II
	AMR	TPE	Grade 2C	III
# reported patients: > 300	**RCT**	**CT**	**CS**	**CR**
BOS	0	0	41(440)	NA
AMR	0	0	5(55)	3(4)

BOS = Bronchiolitis obliterans syndrome; AMR = Antibody mediated rejection

Description of the disease

Chronic lung allograft dysfunction (CLAD) includes multiple disorders, the most common being bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome. Multiple episodes of acute cellular rejection (ACR) put patients at risk for the development of BOS; approximately half of lung transplant patients develop BOS within 5 years. BOS is an obstructive ventilating defect affecting the small airways. BOS can be difficult to diagnose by transbronchial biopsy and thus the diagnosis is typically made based on graft deterioration as assessed by pulmonary function testing (PFTs). It is defined by a sustained (>3 weeks) decline in expiratory flow rates, provided that alternative causes of pulmonary dysfunction have been excluded. According to the International Society for Heart and Lung Transplantation (ISHLT) classification used widely to define the severity of BOS: Category 0 = no significant abnormality and FEV_1 >90% of best postoperative value; potential BOS (0-p) = 81-90% of FEV_1; BOS Category I = 66%-80% of FEV_1; Category II = 51%-65% of $FEV_{1=}$ and Category III = severe BOS with FEV_1 $\leq$50%. The most precipitous decline in airflow typically occurs in the first 6 months following a diagnosis of BOS, although time of onset and rate of decline of FEV_1 are highly variable. Single lung transplantation conveys a higher risk for earlier onset of BOS compared with bilateral transplantation, and unfavorable outcome appears to be associated with rapid onset, female gender, and pre-transplant idiopathic pulmonary fibrosis. Whether antibody mediated rejection (AMR) after lung transplantation exists as an entity has been the subject of debate; recent CRs and CS suggest that AMR should be considered a potential cause of graft dysfunction, particularly when resistance to corticosteroid therapy is encountered.

Current management/treatment

At the time of transplantation, many centers employ an induction regimen that includes infusion of an antibody that targets activated host lymphocytes. Such agents include polyclonal anti-T cell preparations like antithymocyte globulin (ATG), or monoclonal agents aimed at lymphocyte surface molecules such as CD3 (OKT3), IL-2 receptor/CD25 (daclizumab, basiliximab) or CD52 (Campath-1H). Maintenance immunosuppressive therapy after lung transplantation typically consists of a 3-drug regimen that includes calcineurin inhibitor (cyclosporine or tacrolimus), antimetabolite (azathioprine or mycophenolate mofetil), and steroids. Short courses of intravenously pulsed corticosteroids, followed by a temporary increase in maintenance doses for few weeks, are the preferred treatment for uncomplicated acute rejection. The initial treatment of BOS usually consists of repeated pulses of high-dose methylprednisolone. For patients with unresponsive BOS, salvage immunosuppressive regimens have included methotrexate, ATG, or OKT3. The macrolide antibiotic azithromycin has shown efficacy in improving FEV_1 and is frequently prescribed in an adjunctive fashion. A small retrospective CS comparing alemtuzumab to ECP in adult patients with CLAD showed significant improvement in FEV_1 but no difference between the two groups (Moniodis, 2018). Another study reported on 12 adult patients in whom ECP therapy was terminated due to cessation of country-wide insurance coverage; within a year 7 died and the survivors had significant decline in lung function (Robinson, 2017).

Rationale for therapeutic apheresis

Initially, ECP was used in the context of severe, refractory BOS; in which beneficial effect was demonstrated by either stabilization or improvement in FEV_1. More recent literature suggests that ECP may be an effective therapeutic modality for stabilization of lung function in patients with persistent acute rejection and early, less severe stage BOS as well, thus potentially preventing further loss of pulmonary function. There have also been CS reporting lower rates of BOS in patients with ACR who are treated with ECP, suggesting there may be a preventative role for the therapy. Both anti-HLA and "lung-associated self-antigens" (SAgs, tubulin and collagen) have been proposed to have a role in mediating AMR in the lung allograft ("pulmonary capillaritis"). In one study, use of ECP in lung transplant patients was associated with a reduction in the levels of circulating DSA, SAgs and proinflammatory cytokines (Baskaran, 2014). In 2012, the US Centers for Medicare and Medicaid services determined that coverage for ECP in BOS post-lung transplant will be allowed only within the context of a study which involves evidence development. For the treatment of pulmonary AMR (with "pulmonary capillaritis"), few studies have reported use of TPE (typically in combination with IVIG, and anti- B cell/plasma cell therapies) with variable results. In the area of desensitization of highly alloimmunized lung transplant waitlisted patients, use of a multimodal desensitization protocol including TPE, rituximab, bortezomib, steroids, and IVIG in cohort of patients (n = 16) resulted in clearance of DSA in 3 patients, and overall survival was 56% (Vacha, 2017).

Technical notes

One cycle consists of ECP on two consecutive days. In a large CS of ECP in BOS a total of 12 cycles over 6 months were administered: 5 for first month, biweekly for 2 months (4 cycles), and then monthly for 3 months (3 cycles).

Volume treated: Typically, MNCs are obtained from processing 1.5L of whole blood, but the volume processed may vary based on patient weight and HCT. The 2-process method collects and treats MNCs obtained from processing 2 TBV.	**Frequency:** ECP: As above; TPE: Every other day
Replacement fluid: ECP: NA; TPE: Albumin, plasma	

Duration and discontinuation/number of procedures

The optimal duration is unknown. In published studies, the number of treatment cycles for ECP ranged between 6-24. If clinical stabilization occurs with ECP, long-term continuation may be warranted to maintain clinical response. For AMR, treatment may be discontinued upon reversal of rejection or treatment futility.

Keywords: Lung rejection, photopheresis, bronchiolitis obliterans syndrome, pulmonary capillaritis, antibody mediated rejection, desensitization, lung transplantation, plasma exchange

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TRANSPLANTATION, RENAL, ABO COMPATIBLE

Incidence: AMR: 10%, 40% with desensitization; HLA sensitization: 30%	**Indication**	**Procedure**	**Recommendation**	**Category**
	AMR	TPE/IA	Grade 1B	I
	Desensitization, LD	TPE/IA	Grade 1B	I
	Desensitization, DD	TPE/IA	Grade 2C	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
AMR	3(61)	8(342)	NA	NA
Desensitization, LD	0	6(583)	NA	NA
Desensitization, DD	0	0	1(20)	0

AMR = Antibody-mediated rejection; HLA = Human leukocyte antigen; LD = Living donor; DD = Deceased donor

Description of the disease

The use of traditionally immunologically incompatible kidneys has been one of the methods used to expand access to renal transplantation due to conventional donor organ shortage and increased sensitization among prospective recipients. HLA antibodies may be directed to donor specific antigen (DSA). HLA antibodies result from previous exposure to foreign HLAs during transfusions, pregnancy, or transplantation and are a barrier to transplantation because of increased risk for graft loss secondary to hyperacute, acute, or chronic antibody mediated rejection (AMR). Additionally, patients with elevated HLA antibody screen (high PRA) have difficulty finding HLA compatible donors and remain on the transplantation list significantly longer than unsensitized patients. TPE and IA are now used in many transplant centers, to expand access to transplantation through desensitization, i.e., lowering pre-existing antibody titer in the prospective recipients.

AMR has emerged as a leading cause of early and late allograft injury. Diagnosis is based on the Banff classification and relies on 1) DSA detection at the time of rejection, 2) histologic evidence of alloantibody-mediated acute inflammation injury, such as glomerulitis and peritubular capillaritis, and 3) staining of the classical complement remnant C4d in peritubular capillaries. Recipients at higher risk include those with previous transplant and high PRA. Subclinical AMR leads to chronic humoral rejection and late graft loss.

Current management/treatment

New and effective immunosuppressive drugs are continually being developed to prevent and treat acute renal allograft rejection, and to decrease antibody titers. Renal transplant recipients are always placed on immunosuppressive therapy consisting of various groups of medication that affect the cell cycle at different targets. Desensitization regimens typically include IVIG, rituximab, ± additional immunosuppression. Desensitization protocols use low or high dose IVIG, TPE or IA, and/or rituximab to convert a positive to a negative crossmatch to enable transplantation. Bortezomib, a protease inhibitor used to target plasma cells, has been added to some protocols and seems to be effective in treatment of refractory AMR, but results are mixed in desensitization. TPE-based regimens appear to be effective for those awaiting living donor transplants. Transplant after desensitization of high PRA patients has also been performed within the context of kidney paired donations (KPDs; "kidney swaps") and such matching is expected to increase. A multicenter study demonstrated higher survival rate at 1, 3, 5, and 8 years post-transplant in recipients from incompatible donors when compared to patients who either did not undergo transplant or those who waited for transplant from deceased donor (Montgomery, 2011).

AMR treatment has evolved from IVIG to combination regiments using TPE or IA, IVIG, and rituximab. Clinical trials have demonstrated improved graft survival with TPE + IVIG versus TPE alone or IVIG alone, and TPE + rituximab versus TPE alone. A non-randomized study compared high-dose IVIG with TPE + IVIG + rituximab and showed both better graft survival and lower DSA levels post-transplant with the latter (Lefaucheur, 2009). However, use of rituximab has been associated with increased rates of infection.

Rationale for therapeutic apheresis

In AMR, DSA can be removed with TPE, DFPP, and IA. Apheresis is always performed in conjunction with other immunosuppressive drugs. RCTs in the early 1980s did not show TPE to be beneficial when used in combinations with corticosteroids for either acute rejection or acute vascular rejection. CS since 1985 have shown improvement when TPE is used in patients with acute vascular rejection in combination with a variety of anti-rejection medications. This is likely due to improved anti-rejection medications, improved DSA detection, and improved AMR definition using Banff criteria. Previously there was a high graft loss rate with acute vascular rejection; current regimens that include TPE have a graft survival rate of 70-80% (90% in reports with TPE, IVIG, and rituximab).

TPE can also be used prior to transplant to remove HLA antibodies. TPE or IA is used in combination with immunosuppressive drugs pre-transplant until crossmatch is negative. TPE is usually continued postoperatively and re-initiated if AMR occurs. Ability to obtain negative crossmatch depends on DSA titer. AMR risk is ~40% with ~90% 1-year graft survival. Desensitization protocols are appropriate in carefully selected patients.

Technical notes

Volume treated: 1-1.5 TPV	**Frequency:** Daily or every other day
Replacement fluid: Albumin, plasma	

Duration and discontinuation/number of procedures

For AMR, some protocols use a set number of procedures, usually 5 or 6, daily or every other day. Other protocols guide number of treatments based on improvement in renal function and decrease in DSA titers. It is also unclear whether low dose IVIG (100 mg/kg) should be used after every procedure or at the end of the series or not at all.

For desensitization protocols, TPE is performed daily or every other day per protocol until crossmatch becomes negative. TPE is also performed post-operatively for a minimum of 3 procedures. Further treatment is determined by risk of AMR, DSA titers, or the occurrence of AMR.

Keywords: renal transplant, ABO compatible, transplant rejection, desensitization, plasma exchange, immunoadsorption

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TRANSPLANTATION, RENAL, ABO INCOMPATIBLE

Incidence: <1%	Indication	Procedure	Recommendation	Category
	Desensitization, LD	TPE/IA	Grade 1B	I
	AMR	TPE/IA	Grade 1B	II
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	0	0	26(911)	NA

LD = live donor; AMR = antibody mediated rejection

Description of the disease

Due to a relative shortage of compatible organs for renal transplantation, ABO incompatible (ABOi) living donors are used. As of January 6, 2019, >116,545 candidates are on the United Network for Organ Sharing (UNOS) waiting list to receive an allograft, many of these kidneys (95,061). In 2017 (US), 19,849 renal transplants were performed with 31% of patients received kidneys from live donors. Major incompatibility refers to the presence of natural antibodies in recipient against donor's A or/and B blood group antigen(s). These antibodies may cause hyperacute/acute humoral rejection causing endothelial damage (A and B antigens are expressed on vascular endothelium). Major ABOi exists in ~ 35% of random donor-recipient pairs.

Current management/treatment

Most published reports on ABOi solid organ transplantations involve TPE-mediated removal of anti-A or anti-B in conjunction with immunosuppressive treatment (tacrolimus, mycophenolate mofetil, prednisone, daclizumab, rituximab, bortezomib and eculizumab). Other immunotherapy modalities including IVIG and antithymocyte globulins have important roles in the transplant process. Splenectomy, while formerly considered an absolute requirement for ABOi renal transplantation, is no longer necessary. However, it continues to be helpful in the setting of severe refractory rejection. Recently published CRs have used rituximab/eculizumab/bortezomib in ABOi renal transplantation, both prophylactically and treating rejection, but their use varies, and there are no universally accepted protocols for their use. A, B, and AB donor organs have been successfully transplanted with these desensitization strategies. One report suggests that TPE may not be necessary in live donor ABOi renal transplantation if the baseline levels of ABO antibodies are low; however, this approach requires replication in larger studies (Masterson, 2014). ABOi renal transplantation has also been performed within the context of kidney paired donations (KPDs; "kidney swaps") and such matching is expected to increase due to disproportionately long wait times for O recipients. BK virus associated nephropathy (BKVAN) is also a concern in patients receiving ABOi renal transplants and periodic BK virus monitoring is recommended.

Natural occurrence of the A2 blood type, which has reduced expression of the A antigen on RBCs and endothelium, has been exploited in transplantation; A2 donors are preferred over group A1 donors in group O or B recipients in living donor kidney transplantation as they have a lower risk of graft rejection. UNOS permits A2/A2B deceased donor kidney transplantation into B recipients if certain anti-A titer requirements are met, without the need for TPE. Published evidence suggests that outcomes of such transplants are equivalent to ABO-compatible deceased donor transplants.

Rationale for therapeutic apheresis

While there are no controlled clinical trials on use of TPE to facilitate ABOi renal transplantation, an abundance of supportive evidence exists. Given that hyperacute rejection and acute antibody mediated rejection are risks in ABOi renal transplants, TPE has been used as key therapeutic modality to reduce anti-A and/or anti-B titers in peri-transplant period with goal of preventing rejection and facilitating graft survival. Both short and long-term ABOi kidney transplant survival statistics compare well with that seen in ABO-compatible transplants. In ABOi kidney transplantation, TPE is used to lower antibody titers below a critical threshold (which differs based on titration method/ technique) prior to the transplant procedure. Apart from TPE, DFPP and ABO-antigen specific and non-specific IA columns have been used (outside the US) to remove ABO antibodies.

Technical notes

The replacement fluid for TPE is albumin or plasma (plasma should be compatible with both the recipient and donor ABO type), depending upon presence of coagulopathy. In the immediate pre- and post-surgical setting, plasma is typically used. One study reported a higher incidence of early bleeding complications among ABOi renal transplant patients, and close monitoring of coagulation status is recommended (Lentine, 2014).

Volume treated: 1 - 1.5 TPV	**Frequency:** Daily or every other day
Replacement fluid: Albumin, plasma	

Duration and discontinuation/number of procedures

The goal should be to reduce the antibody titer to less than critical threshold prior to taking patient to transplant. It is important to note that this threshold titer will need to be determined by each program, given that titer results can vary widely depending on titration method and technique used. The number of TPE procedures required depends upon baseline IgG titer, and on rate of antibody production/rebound. Most AMR episodes occur within the first 2 weeks following transplantation. Post-transplant ABO titers have low positive predictive value and high negative predictive value for diagnosis of AMR (Tobian, 2010). Several ABOi programs utilize biopsies to monitor the allograft for histological signs of rejection prior to TPE discontinuation, although this practice is not universal. Of note, C4d positivity is very common in ABOi transplant renal biopsies; however, this is not necessarily indicative of humoral rejection unless accompanied by light microscopic changes suggestive of rejection.

Keywords: ABO incompatible renal transplantation, renal transplantation, renal desensitization, renal rejection, plasma exchange

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VASCULITIS, ANCA-ASSOCIATED (AAV)

Incidence: 1-3/100,000/yr (geographical and ethnic differences; MPA: 48-65%, GPA: 25-40%, EGPA: 10-12%)	**Indication**	**Procedure**	**Recommendation**	**Category**
	MPA/GPA/RLV			
	RPGN, Cr ≥5.7 mg/dl*	TPE	Grade 1A	I
	RPGN, Cr <5.7 mg/dl*	TPE	Grade 2C	III
	DAH	TPE	Grade 1C	I
	EGPA	TPE	Grade 2C	III
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	10(1091)	5(345)	NA	NA

MPA = microscopic polyangiitis; GPA = granulomatosis with polyangiitis; EGPA = eosinophilic granulomatosis with polyangiitis; RLV = renal-limited vasculitis; RPGN, rapidly progressive glomerulonephritis; DAH = diffuse alveolar hemorrhage;
*Cr thresholds for renal function at presentation adopted from Yates, 2016; Cr ≥5.7 mg/dl includes "on dialysis".

Description of the disease

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is defined as necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels. ANCA can be specific for myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA). AAV is clinically subdivided into MPA, GPA, the most infrequent and clinically separate entity of EGPA, and RLV. Overlapping features between AAV subtypes occur. Besides the clinical diagnosis, ANCA specificity separates patients into groups with different relapse risk and treatment response. AAV can affect any organ but commonly involves the kidneys in 70%, typically exhibiting RPGN with high risk of end stage renal disease (ESRD), lungs (>50% at onset), ear-nose-throat, joints, skin and nerves. Worse renal prognosis is predicted by AAV histology classification with tubule-interstitial fibrosis and atrophy, and in MPO-ANCA positive patients. Lung involvement can range from asymptomatic pulmonary lesions to life-threatening DAH. EGPA hardly ever is associated with RPGN or DAH. The presentation of the pulmonary-renal syndrome associated with ANCA can be clinically similar to anti-glomerular basement membrane (GBM) disease (Goodpasture's Syndrome). When ANCA and anti-GBM are both present, the disease should be considered to represent anti-GBM disease (see separate fact sheet).

Current management/treatment

Mortality of AAV has been fundamentally improved over the last 5 decades by the use of steroids and immunosuppressants. The long-term course is now largely determined by the frequency of disease flares and by accruing damage caused by disease activity and treatment related complications. The treatment of all AAV subtypes is usually divided into two phases, i.e., induction of remission and maintenance of remission. Urgent treatment is required to prevent irreversible organ damage. Standard induction treatment of AAV includes steroids, cyclophosphamide and rituximab, inducing remission in up to 90% at 6 months. Leflunomid no longer plays a substantial role; bortezomib or blocking of C5a-receptors, or, for EGPA, mepolizumab (anti-IL5), may become future options. Maintenance treatment usually entails low-dose steroids plus an additional immunomodulatory therapy (azathioprine, mycophenolate mofetil, or rituximab) for 12-18 months. The safety of rituximab has become a topic of major attention with its increasing use in both remission induction and maintenance therapy, thus reducing the toxicity from cumulative doses of cyclophosphamide and ongoing maintenance therapy. However, its long-term safety is still being debated. Infection related morbidity and mortality due to immunosuppressive therapy remains a significant issue in AAV. Therefore, individual risk-benefit analysis is a major principle for any treatment of AAV.

Rationale for therapeutic apheresis

The pathogenic role for ANCAs underlies the scientific rationale for therapeutic apheresis in the treatment of AAV. The characteristic acute lesion is localized vessel wall necrosis, which releases constituents of the plasma into the necrotic zone, where thrombogenic factors activate the coagulation cascade. Due to the complexity of these plasmatic changes and the existence of ANCA-negative AAV, putative equivalence of TPE and IA remains in question (Stegmayr, 1999). Before the clear ANCA guided definition of AAV, clinical studies on TPE enrolled patients by the clinical syndrome of RPGN, which is not exclusive for AAV. A meta-analysis of these trials concluded, that additional use of TPE may reduce the composite of ESRD or death (Walsh, 2011). The addition of TPE was recommended to increase the chance of renal recovery, if renal function is severely impaired (defined as Cr ≥5.7 mg/dL or requirement of dialysis). TPE in patients with AAV and DAH has a weaker evidence, however, retrospective analyses reported clinically relevant benefit (Uechi, 2018). For EGPA in general, due to its low incidence and separate clinical characteristics, the evidence base for the use of TPE is substantially weaker (Groh, 2015).

The MEPEX trial with a total of 137 AAV patients presenting with Cr >500 μmol/L (5.7 mg/dL) or requiring dialysis, demonstrated that 7 TPE sessions additional to oral cyclophosphamide and oral corticosteroids, when compared to pulse methylprednisone (1000 mg/day × 3 days), increased the rate of renal recovery at 3-12 months without a benefit for survival (Jayne, 2007). In dialysis-dependent patients, TPE was superior with respect to the chance of coming off dialysis (de Lind van Wijngaarden, 2007). After a median of almost 4 years follow-up, there was no longer a net benefit of TPE in clinical outcomes (Walsh, 2013). Also, in subsequent non-randomized CTs or CSs benefit of TPE was not always confirmed. The PEXIVAS trial evaluated TPE in 704 patients with GPA or MPA with pulmonary hemorrhage and/or severe renal disease (Walsh, 2013). All patients received induction therapy with a steroid pulse and cyclophosphamide or rituximab and were randomized to receive seven or no TPEs and two different steroid dose regimens. Preliminary results confirmed a transient benefit regarding the composite of ESRD and death in the first year, which like in the MEPEX trial disappeared with further follow-up (Walsh, 2018). Although PEXIVAS failed to show a benefit of TPE, it does not exclude a clinically useful benefit in further sub-analyses. Editorial deadline of this fact sheet was before the full publication and meta-analysis of data with previous studies were available, which might necessitate future modification of recommendations.

Technical notes

In patients with DAH, replacement with plasma is recommended to avoid additional bleeding risk.

Volume treated: 1-1.5 TPV **Frequency:** Daily or every other day

Replacement fluid: Albumin; plasma when DAH present

Duration and discontinuation/number of procedures

Median number of TPE is 7 over a median period of 14 days, up to 12 are reported to result in further improvement in patients with severe renal failure or DAH (deLuna, 2015).

Keywords: ANCA, MPO-ANCA, PR3-ANCA, ANCA associated vasculitis, granulomatosis with polyangiitis; Wegener's granulomatosis, diffuse alveolar hemorrhage, rapidly progressive glomerulonephritis, microscopic polyangiitis, pauci-immune glomerulonephritis, plasma exchange, plasmapheresis, immunoadsorption

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VASCULITIS, IgA (HENOCH-SCHÖNLEIN PURPURA)

Incidence: 13-22/100,000 with 1% developing RPGN	**Indication**	**Procedure**	**Recommendation**	**Category**
	Crescentic RPGN	TPE	Grade 2C	III
	Severe extrarenal manifestations	TPE	Grade 2C	III
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	9(72)	22(25)

RPGN = Rapidly progressive glomerulonephritis

Description of the disease

Henoch-Schönlein purpura (HSP), newly named IgA Vasculitis (IgAV) or IgA vasculitis with nephropathy (IgAVN) and in severe cases, crescent IgAVN (CreIgAVN), is the most common systemic vasculitis in childhood; 95% of HSP cases occur in children. HSP is almost always a self-limiting disorder, unlike most other forms of vasculitis. It presents with arthralgia/arthritis, abdominal pain, kidney disease, and palpable purpura in the absence of thrombocytopenia or coagulopathy. Characteristically, it occurs following an upper respiratory tract infection. The highest incidence of HSP is in Caucasians while African Americans have the lowest incidence. HSP is a systemic small vessel vasculitis characterized by deposition of IgA-containing immune complexes within tissues. In IgAVN it is thought that Anti IgA1 autoantibodies play a central role in the pathomechanism. Due to an inherited or acquired glycosylation defect in the mucosa of the GI, galactose deficient IgA1 (GdIgA1) is produced. These immuncomplexes are bound to the transferrin receptors of the mesangium causing mesangium cell proliferation and activation of neutrophils. IgA from serum of IgAV patients has been found to bind to human endothelial cells in vitro, supporting the presence of IgA anti-endothelial cell antibodies (AECA). It has been hypothesized that microorganisms have similar antigenic structures as human vessel walls. Infection with these microorganisms could lead to the production of cross-reactive AECA, although no specific microorganism has been identified in IgAV yet (Heineke, 2017).

All patients develop palpable purpura. In the skin, immune complex deposits lead to subepidermal hemorrhages and small vessel necrotizing vasculitis producing the purpura. One-quarter to one-half of cases involve the kidney. Necrotizing vasculitis leads to organ dysfunction or hemorrhage in other organs. In adults, the clinical presentation is more severe, and outcomes are worse. Serum IgA levels were elevated in 60% of cases in one large adult CS. Nonetheless, the precise role of IgA or antibodies to it in the pathogenesis of the disease remains unclear. In adults, the presence of interstitial fibrosis and glomerulosclerosis on kidney biopsy carries a poor prognosis. Reports of end stage renal disease (ESRD) range from 15-30% over 15 years of age with additional cases advancing to stage IV chronic kidney disease. A small percentage of patients will develop significant extrarenal dysfunction including cerebritis or severe GI bleeding.

Current management/treatment

Treatment is supportive care including hydration, rest, and pain control. In patients with severe kidney involvement (CresIgAVN) or severe symptoms of vasculitis, treatment can also include corticosteroids with or without immunosuppressants such as cyclophosphamide, azathioprine, or cyclosporine and IVIG. If ESRD develops, kidney transplantation may be necessary.

Rationale for therapeutic apheresis

The rationale for TPE is the removal of IgA1-containing immune complexes or IgG autoantibodies. Early positive experiences of the use of TPE in treating some forms of RPGN resulted in the application of TPE to HSP when crescentic glomerulonephritis developed in the disease. In addition, because of the use of TPE to treat severe sequelae of other forms of vasculitis, TPE has also been used to treat severe GI or skin manifestations and cerebritis in HSP. Numerous CRs have demonstrated some success in severely ill patients with IgAV or IGAVN and severe bleedings of the lung, GI tract and in cerebritis.

Limited but encouraging data suggest TPE may benefit patients with severe disease. Seven CRs and 8 CS totaling 67 patients have examined the use of TPE in treating CreIgAVN in the setting of HSP. In 27 of these patients, concurrent immunosuppressive therapy was not given. In these patients treated with only TPE, 21 had complete resolution of their renal disease, 2 had persistent hematuria, 1 had persistent proteinuria, and 2 progressed to ESRD. The remaining patient was an adult who had resolution of renal disease with TPE but recurrence following discontinuation of TPE. The patient subsequently had complete resolution of renal disease with TPE and cyclophosphamide. Of the 40 patients treated with TPE and corticosteroids and/or immunosuppressants, all were reported to have had resolution of renal disease.

Technical notes

Replacement fluid has varied depending upon the clinical situation with the final portion consisting of plasma in the presence of severe bleeding. DFPP has also been used in a single patient with RPGN in HSP with resolution of renal disease (Chen, 2004).

Volume treated: 1-1.5 TPV	**Frequency:** 4-11 over 21 days
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

In severe manifestations, the course of therapy has ranged from 1-11 TPE daily with discontinuation of TPE upon resolution of symptoms. In CreIgAVN, longer courses of therapy have occurred with therapy discontinued with improvement in renal function as determined by creatinine measurement.

Keywords: plasma exchange, Henoch-Schönlein purpura, rapid progressive glomerulonephritis

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VASCULITIS, OTHER

Incidence: PAN: 5-77/1,000,000; Behçet's Disease: 7-370/100,000		**Indication**	**Procedure**	**Recommendation**	**Category**
		HBV-PAN	TPE	Grade 2C	II
		Idiopathic PAN	TPE	Grade 1B	IV
		Behcet's disease	Adsorptive cytapheresis	Grade 1C	II
		Behcet's disease	TPE	Grade 2C	III
# reported patients: >300		**RCT**	**CT**	**CS**	**CR**
HBV-PAN	TPE	0	0	1(115)	NA
Idiopathic PAN	TPE	2(140)	1(342)	NA	NA
Behcet's disease	Adsorptive cytapheresis	0	0	2(18)	2(3)
Behcet's disease	TPE	0	0	1(4)	3(3)

PAN = polyarteritis nodosa; HBV = hepatitis B

Description of the disease

Vasculitis involves inflammation in blood vessels including arteries, veins, and capillaries. There are other types of vasculitis addressed in this issue (see separate fact sheets). Polyarteritis nodosa (PAN) is a form of vasculitis that mainly affects medium-sized arteries, frequently presenting with peripheral neuropathy, skin, renal, and other organ and system manifestations, some of these are non-specific: weight loss, fever, myalgia, rash, neuropathy, or abdominal ischemia. It typically spares pulmonary and glomerular arteries. It may also involve single organ or skin only. PAN is not associated with anti-neutrophil cytoplasmic antibodies (ANCA). It can be idiopathic or associated with infection such as hepatitis B virus (HBV). People between 40 and 60 years are most often affected. There is no specific test to diagnose PAN.

Behçet's disease (BD) is a rare immune-mediated systemic vasculitis that can involve blood vessels of all sizes and can affect both the arterial and venous vessels. It is a chronic relapsing-remitting immuno-inflammatory disorder with a variety of clinical manifestations including urogenital ulceration, and ocular, vascular, central nervous system, articular, mucocutaneous, and gastrointestinal symptoms. It is found primarily in Asia along the ancient silk-road and with high prevalence in individuals with HLA B51. Most manifestations are self-limiting, but repeated attacks of uveitis are a major cause of blindness. Ocular BD and CNS BD are often associated with the highest morbidity and mortality.

Current management/treatment

For HBV-PAN, treatment includes glucocorticoids, anti-viral medications, and TPE. Because of effective HBV vaccination, HBV-PAN is uncommonly seen. For idiopathic PAN, treatment consists of glucocorticoids and immunosuppression such as cyclophosphamide. The Five-Factor Score (FFS) has been used for PAN for evaluating disease severity and prognosis. Patients with renal symptoms, gastrointestinal tract involvement, cardiomyopathy, central nervous system involvement, loss of >10% of body weight, and age >50 years may have poor prognosis and require maintenance treatment. Current management of BD includes topical medication, systemic steroids, antibiotics, and immunosuppressive and anti-inflammatory agents. Biologic agents such as infliximab and secukinumab have shown promise in small trials particularly for mucocutaneous and neurologic manifestations (Fernando, 2014; Di Scala, 2018). TPE and granulocyte and monocyte adsorption apheresis have also been tried with some success in small CS and CRs.

Rationale for therapeutic apheresis

Pathogenesis of HBV-PAN has been attributed to immune complexes which may be removed by TPE. The combination of TPE, steroids, and antiviral agents has been shown to be effective in several CS for HBV-PAN. In one study, 115 patients received TPE and immunosuppression, some also received anti-viral medication. At a mean follow-up of 69 months, 93 patients (81%) were in remission, 22 (19%) did not achieve remission and had died (Guillevin, 2005). Several RCTs have not shown any additional benefit of TPE to corticosteroids in reducing relapse rates for idiopathic PAN (Guillevin 1992; Guillevin, 1995). The first RCT was performed in 60 patients with PAN (excluding HBV-PAN) and demonstrated that the prednisone and TPE combination was no more effective than corticosteroids alone in preventing relapses over the long-term (Guillevin, 1992).

TPE may remove immune complexes in BD. Adsorptive cytapheresis, specifically adsorption granulocytapheresis, may remove NK cells or other cells that are implicated in the inflammatory response in BD. In one study, 9 out of 14 (64%) patients with refractory ocular BD who underwent granulocytapheresis showed improvement, and patients who had a long duration of disease are better responders (Namba, 2006).

Technical notes

Volume treated: 1 TPV	**Frequency:** See below
Replacement fluid: Albumin	

Duration and discontinuation/number of procedures

For HBV-PAN, 9-12 TPEs (over 2-3 per week) have been used. For ocular BD, 5 granulocytapheresis sessions performed at 1 session/week over 5 consecutive weeks have been used.

Keywords: Vasculitis, polyarteritis nodosa, eosinophilic granulomatosis with polyangiitis, Churg-Strauss syndrome, Behçet's disease, plasma exchange, adsorption granulocytapheresis

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VOLTAGE-GATED POTASSIUM CHANNEL (VGKC) ANTIBODY RELATED DISEASES

Incidence: Rare		**Procedure**	**Recommendation**	**Category**
		TPE/IA	Grade 1B	II
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	1(21)	7(38)	31(34)

Description of the disease

VGKCs are membrane proteins expressed by a wide range of cells but are most important in the control of membrane excitability in the nervous system. Proteins representing integral parts of the VGKC-complex are the target antigens for VGKC antibodies, including leucine-rich, glioma inactivated 1 (LGI1), contactin-associated protein-2 (CASPR2), and contactin-2. VGKC complex antibodies were initially described in adults with limbic encephalitis, which clinically represents a prototype of antibody mediated encephalitis (AME) if associated with NMDAR-antibodies (Dalmau, 2018; see separate fact sheet). LGI1-AME is the second most common AME with an incidence 0.8 per million persons. Patients who test positive for VGKC autoantibodies are frequently positive for antibodies to one or more of those antigens. Antibodies also appear in cerebrospinal fluid. VGKC-complex antibodies are implicated in the pathogenesis of acquired neuromyotonia (NMT), LGI1/CASPR2-AME, and Morvan's syndrome (MVS). Paraneoplastic appearance in some patients (~20%) complicates evaluation and final diagnosis. LGI1/CASPR2-AME is characterized by memory loss presenting as dementia, faciobrachial dystonic seizure, insomnia, dysautonomia, or ataxia. Peripheral nerve hyperexcitability without exertional weakness, and muscle stiffness are chief manifestations of NMT. MVS, which is a male dominant entity, typically presents with NMT, neuropsychiatric features, autonomic dysfunction, and neuropathic pain, thus overlapping with AME or NMT. Overall, the long-term prognosis is highly variable ranging from spontaneous remission to fatal cases. CASPR2 antibodies associated with a thymoma might indicate poor prognosis. VGKC-complex antibodies have been also detected in more isolated neurologic symptoms, including autonomic dysfunction, chronic epilepsy, peripheral neuropathy, motor neuron disease, dementia, and depression. However, the clinical significance in this group of disorders is less clear.

Current management/treatment

The wide spectrum of clinical presentations makes differential diagnosis complex and many patients suffer from the delayed recognition of these conditions. Since the discovery of VGKC antibodies, some conditions, in particular encephalitis, previously considered only for symptomatic treatment, have received better explanation of pathogenesis based on interaction of the autoantibody with the VGKC receptor on cell membranes in the central and peripheral nervous system. Thus, different immunotherapies have been used in VGKC-complex antibody associated diseases, including the entire multimodal therapeutic armamentarium against autoantibody-associated diseases (e.g., steroids, IVIG, therapeutic apheresis (TPE, or IA), immunosuppressive drugs and B cell antibodies like rituximab), in addition to symptomatic treatment (e.g., anti-seizure medication). Due to the overall low incidence of VGKC-complex antibody associated diseases the evidence for all options is limited. Application of steroids is regarded fundamental in any combination therapy. For AME in general, thus including VGKC-AME, TPE, or if available IA, is increasingly used as first-line treatment combined with steroids, and symptomatic drug treatment. Acute therapy for MVS or NMT usually consists of steroids and/or IVIG. TPE, or IA is considered as a second-line option. Of note, most recent CS have reported that early diagnosis and initiation of immunomodulation therapy have led to better control of symptoms such as seizures, which are often resistant to conventional anti-seizure medications. In general, non-paraneoplastic syndromes show a better response to immunomodulating therapies. Due to the high variability of symptoms, response to treatment, and outcome, treatment needs to be individualized.

Rationale for therapeutic apheresis

There is a clear rationale for the use of TPE, or IA as part of the multimodal immunomodulating therapeutic approach, as the rapid decrease of VGKC antibodies with TPE, or IA is associated with clinical improvement. An open label prospective study used an immunotherapy protocol consisting of IV methylprednisolone (1 g/day for 3 days), TPE of 5 treatments over 7-10 days typically after completion of IV methylprednisolone, followed by IVIG (2 g/kg over 5 days) and maintenance therapy with oral prednisolone (1 mg/kg). Using this regimen on 9 patients (first 3 patients also received MMF at 2 g/day) they reported improvement in all treated patients with clinical remission ranging from 4-40 months, normalization of changes on magnetic resonance imaging, and significantly decreased VGKC antibody levels (Wong, 2010). In a two-center retrospective analysis of 10 patients with VGKC-AME, TPE was administered in 7 patients in conjunction with steroids and IVIG. Four of 7 patients reported complete resolution and 2 of 7 reported slight improvement. It was noted that early steroid administration was associated with faster decrease in antibody titers (Vincent, 2004). In a CS of 5 retrospectively identified patients with neurological symptoms and VGKC antibodies treated with TPE, there was a durable clinical response in 3 of these patients (Jaben, 2012). Moreover, in some of the reports, TPE was used as a chronic therapy to maintain low antibody levels and to control symptoms. The frequency of maintenance TPE varied from a limited course of 10 TPEs over 5 weeks to open-ended treatment ranging from 1 TPE/every 3 weeks to every 3 months. Successful use of IA was reported for VGKC-AME cases including a case control study comparing TPE and tryptophan-IA, thus avoiding replacement of human plasma products with their potential side effects or cost.

Technical notes

Volume treated: 1-1.5 TPV with TPE; 2-2.5 liters for tryptophan-IA (manufacturer's recommendation); up to 2.5 TPV with regenerative immune adsorbers.

Frequency: 5-10 treatments with TPE or IA over 7-14 days adjusted to the individual curse.

Replacement fluid: Albumin for TPE; none for IA.

Duration and discontinuation/number of procedures

Anti-VGKC titers often correlate with symptoms' severity. Thus, serial measurements of those titers are often performed after the series of treatments to monitor disease activity and evaluate response. However, response of clinical symptoms has been used to determine treatment course.

Keywords: voltage-gated potassium channel antibodies, LGI1, CASPR2, Morvan syndrome, neuromyotonia, limbic encephalitis, autoimmune encephalitis, plasma exchange, immunoadsorption

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WILSON DISEASE, FULMINANT

Incidence: Rare		**Procedure**	**Recommendation**	**Category**
		TPE	Grade 1C	I
# reported patients: <100	**RCT**	**CT**	**CS**	**CR**
	0	0	3(15)	22(23)

Description of the disease

Wilson disease is an autosomal recessive genetic disorder resulting from a mutation in the *ATP7B* gene, which encodes a copper transporting ATPase protein, leading to impaired biliary copper excretion, resulting in copper accumulation in the liver, brain, cornea, and kidney. Copper's incorporation into ceruloplasmin is also impaired. Birth incidence rates are 1/30,000-40,000. It has been estimated that ~1% of the population are carriers. The disease usually presents between ages 5-35 years. Children present with asymptomatic liver deposits of copper; teenagers with liver disease; and adults with neurological symptoms. The spectrum of liver disease includes asymptomatic liver function test (LFT) abnormalities, hepatitis, cirrhosis, and acute liver failure (ALF). Neurological symptoms include Parkinsonism, dystonia, cerebellar and pyramidal symptoms. History of behavioral disturbances is present in half of patients with neurological disease. The appearance of Kayser-Fleischer rings (copper deposits in the outer rim of the cornea) and direct antiglobulin test (DAT) negative hemolytic anemia are relatively common. The hemolysis appears to be primarily due to copper-induced oxidant stress to RBC enzyme pathways and membrane damage. ALF is typically accompanied by hemolytic crisis and multiorgan failure with rapid clinical deterioration and is nearly always fatal without liver transplantation (LT). No laboratory test is diagnostic but suggestive results include low serum ceruloplasmin, increased 24-hour urinary copper excretion, and elevated serum copper. The gold standard for diagnosis is a liver biopsy showing elevated copper content. A genetic test for *ATP7B* gene mutations is also available.

Current management/treatment

Asymptomatic patients should be treated, since the disease is almost 100% penetrant. Low-copper diets are recommended. Zinc acetate is non-toxic and stimulates metallothionein, which reduces dietary and enterohepatic absorption of copper. It is the therapy of choice for asymptomatic patients or patients with hepatitis or cirrhosis, but without evidence of hepatic decompensation or neurologic/psychiatric symptoms. Zinc is also first choice in pediatric and pregnant patients. Chelation therapy (penicillamine, trientine) increases urinary copper excretion. Trientine has replaced penicillamine as the primary chelator due to less toxicity. If penicillamine is given, it should always be accompanied pyridoxine (25 mg/day). Chelation can be used as a temporizing agent to treat the enormous release of copper into the blood stream in ALF with renal failure; however, substantial removal is not achieved for at least 1-3 months. Other methods have been used to reduce copper load to stabilize patients including hemofiltration, albumin dialysis and the Molecular Adsorbents Recirculating System (MARS). For initial neurologic therapy, tetrathiomolybdate is emerging as the drug of choice because of its rapid action, preservation of neurologic function, and low toxicity. It has gone through a successful phase II clinical trial in the US and Europe. Copper reduction therapy must be life-long. LT is potentially curative and is the main stay of therapy for patients with ALF. Disease severity is estimated using one of various existing prognostic scores, which are based on a combination of laboratory values, most commonly LFTs and coagulation status (INR/PT); New Wilson's index, Child-Pugh score and model for end-stage liver disease (MELD) score. LT reverses most of the clinical and biochemical pathological manifestations of the disease within few months.

Rationale for therapeutic apheresis

Donor organs for LT are not always available and temporizing treatments must be aimed at treating the release of massive amounts of copper into circulation. In this scenario, TPE can be beneficial as it rapidly removes significant amounts of copper from the circulation, an average of 20 mg per TPE treatment. Decreased serum copper may decrease hemolysis, prevent progression of renal failure and provide clinical stabilization. TPE can also remove large molecular weight toxins (aromatic amino acids, ammonia, endotoxins) and other factors, which may be responsible for hepatic coma. In most reported cases, TPE was used as a bridge to LT. Interestingly, recent reports showed that TPE combined with chelating agents improved ALF and eliminated the need for LT. In addition, the widespread availability of TPE over MARS or equivalent technology makes it a more accessible choice of therapy.

Technical notes

Plasma replacement rapidly corrects coagulopathy. Plasma/albumin combination is also possible. Use of albumin alone will worsen coagulopathy.

Volume treated: 1-1.5 TPV	**Frequency:** Daily or every other day
Replacement fluid: Plasma, albumin	

Duration and discontinuation/number of procedures

Serum copper reduction in most CRs had been achieved rapidly and maintained after the first 2 treatments. However, the total number of TPE performed is variable (1-11), depending on LT availability or recovery. Specific laboratory tests for the disease (e.g., serum copper, 24-hour urinary copper excretion) are not routine testing and thus, are not helpful to guide effectiveness and the frequency of the treatment. In most cases, judgment is based on clinical parameters and routine testing (i.e., improved encephalopathy, LFTs and controlled hemolysis).

Keywords: Wilson's disease, liver transplantation, copper, plasma exchange

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